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OBSERVATIONS ON CAROTENEMIA*

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YELLOWISH pigmentation of the skin (*xanthodermia*) is most commonly due to jaundice; it is then accompanied by characteristic changes in the mucous membranes, blood, urine and feces. It is, however, seen also when substances such as picric acid, saffron and mepacrine are ingested and stain the tissues. In Great Britain during World War II, when fats were in short supply, xanthodermia was met not infrequently, due to an excessive intake of carrots which followed an exhortation from the Ministry of Food on their virtues. This condition of carotenemia had been earlier described under the names *aurantiasis* and *carotenosis cutis,* but it was regarded as a rare phenomenon.

It was the occurrence of hypercarotenemia during this period, and the fact that my colleague, Professor R. A. Morton, was working in the biochemical field of carotenoids and vitamin A, which stimulated an investigation on the clinical types of carotenemia.

CAROTENOIDS

Carotenoids are pigments of plant origin, and there is no evidence that animals can synthesize them from simpler compounds. Karrer, Kuhn and their collaborators have established the structural formulae of the principal carotenoids. Their general formula is $C_{40}H_{56}O_n$, where n is 0–6. The hydrocarbons (here $n = 0$) are termed *carotenes,* and the hydroxyl derivatives, *xanthophylls.*

The carotenoids occur in all green vegetables and especially carrots, and are also found in butter, eggs and oranges. (Goodwin [4] gives complete

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analyses of the carotenoid content of various foods.) Beta-carotene is the most important precursor of vitamin A; it comprises 10 to 30% of the total pigment and is often accompanied by cryptoxanthin (3-hydroxy-beta-carotene), another vitamin A precursor. In animals vitamin A is stored chiefly in the liver but to a lesser extent in the kidney. It is mainly in the form of an ester but is liberated continuously in small amounts into the blood-

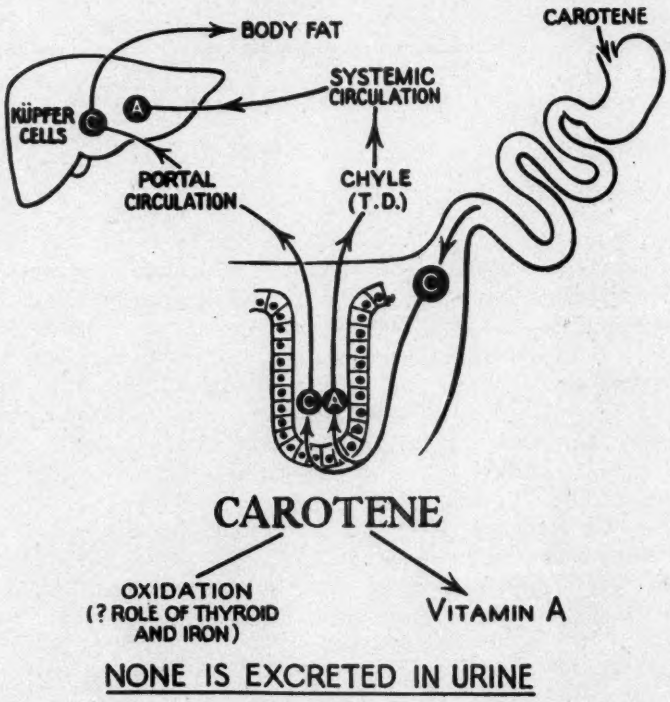

FIG. 1. Shows ingestion of carotene (C); followed by (a) absorption to storage in liver and body fat and (b) conversion into vitamin A (A) in intestinal mucosa, then absorption through thoracic duct and storage in liver.

stream as free vitamin A alcohol. Normally there are 100 μg. of carotenoids per 100 ml. of blood, and the xanthophyll : carotene ratio is 2 : 1. The earlier name of *lipochromes* points to their fat solubility.

Moore [7] was the first to demonstrate that carotene is a vitamin A precursor. He recorded an increase in the level of the vitamin A stores of rats receiving carotene, and it was assumed that the liver was the site of conversion, though there can be no doubt from recent work that the main conversion into vitamin A is extrahepatic and occurs in the intestinal mucosa (figure 1), though this is not the exclusive site. The amount of beta-carotene absorbed from different foodstuffs varies with their nature; for example, it is less from

non-fatty foods. Mineral oils such as liquid paraffin seriously reduce carotene absorption. (For a comprehensive discussion of this problem see Lowe and Morton [6] and Morton and Goodwin.[8])

There is evidence that absorption of beta-carotene varies directly with thyroid activity in some species, though it may well be that this is an indirect effect, for a rat with hyperthyroidism may accumulate more vitamin A than a normal rat, either because improved absorption of beta-carotene means that more is presented to the enzyme system responsible for the conversion, or, alternatively, that the thyroid hormone renders the enzyme system more effective.

The normal range of vitamin A in the blood is 120 to 150 i.u. per 100 ml., and deficiency symptoms, especially of dark adaptation, tend to appear when the level remains below 50 i.u. per 100 ml. for a year or longer.

Carotenemia Due to Excessive Ingestion

We have observed 50 cases of well marked hypercarotenemia due to a raw carrot intake of from four to eight pounds daily. Most of these were seen during World War II, but a few were observed both before and since. In recent years a raw carrot diet to induce slimming has been a prominent cause. Xanthodermia tended to appear after about six to eight months, but if carrots were then omitted from the diet the yellowish tinge faded in from two to six weeks. The main sites of the pigmentation were the face (especially the nasolabial folds) and the palms and soles. The mucous membranes and conjunctivae were clear, and no carotene was found in the urine. There were no subjective symptoms, and the patients were usually referred with "jaundice" or "anemia."

The excessive carotene in the blood can be demonstrated and differentiated from jaundice by the simple method of Greene and Blackford [5]: "Equal volumes of serum, absolute alcohol, and petroleum ether are shaken together in a test-tube, and left to stand. In carotenemia, the top layer of petroleum ether shows a yellowish discoloration. In jaundice, it is in the middle layer of alcohol that the bile pigments are dissolved and these often colour also the bottom layer of precipitated proteins." Carotene often rose to 500 μg. per 100 ml. in this group of cases; the xanthophyll: carotene ratio remained more than 1, and vitamin A was always present in excess, though the blood lipids were normal.

Carotenemia in Diabetes Mellitus

Before the introduction of insulin the most marked examples of carotenemia were seen in severe diabetics, especially in children who were on a severely restricted carbohydrate diet which consisted largely of "5%-carbohydrate" green vegetables. Here excessive intake was clearly the prime but not the only cause, for even without excessive intake a diabetic may show carotenemia. A possible explanation is the accompanying hyperlipemia, for

in many hyperlipemic xanthomatoses, and in nephrotic states, carotenemia is commonly found.

Case 1. This patient was a 27 year old female with *familial xanthomatosis palpebrarum* and carotenemia. Blood analysis showed:

Vitamin A	77	i.u./100 ml. plasma
Carotenoids. Total	243	μg./100 ml. plasma
Carotene	70	μg./100 ml. plasma
Xanthophyll	130	μg./100 ml. plasma
Total lipid (two hours after food)	1.19	gm./100 ml. plasma

Case 2. This patient was a 16 year old boy with *a nephrotic syndrome.* Blood analysis showed:

Vitamin A	86	i.u./100 ml. plasma
Carotenoids. Total	259	μg./100 ml. plasma
Carotene	76	μg./100 ml. plasma
Xanthophyll	160	μg./100 ml. plasma
Total lipids (fasting)	1.30	gm./100 ml. plasma
Cholesterol	340	mg./100 ml. plasma

It is, however, interesting to note that Rosenberg and Sobel [9] showed that alloxan-diabetic rats had an impaired capacity to convert beta-carotene into vitamin A in the isolated intestinal mucosa. If this were true of the human diabetic it might explain in part the carotenemia, but there is no evidence of associated vitamin A deficiency in the diabetic as there is in the patient to be described later, in whom carotenemia is demonstrably associated with vitamin A deficiency.

Carotenemia in Myxedema

It is more than 20 years since Escamilla et al.[8] described carotenemia in myxedema, and this has been amply confirmed since. For example, in two patients under the care of Cadman and myself the following changes were found:

Table 1

Carotenemia in Myxedema

Case	Date	Carotenoid μg.%	Carotene μg.%	Vitamin A μg.%	Cholesterol mg.%	Thyroid Condition	Note
S.	July '51	375	145	46	605	Myxedema	Untreated
	May '52	105	—	28	198	Almost euthyroid	Treated
	Nov. '52	76	—	23	147	Normal	
H.	Oct. '53	119	31	33	409	Myxedema	Untreated
	3 wks. later	62	18	29	250	Much improved	Treated

The mechanism whereby these changes occurred engaged our attention, and Cadman [1] undertook a study of the influence of dysthyroidism on the blood carotene and vitamin A to decide whether the thyroid hormone plays a significant part in the conversion of carotene into vitamin A.

Carotene and Thyroid Function

Reference was made earlier to the fact that in certain species the thyroid hormone aids the absorption of carotene from the intestine, though this has not been shown in man.

The factors which have been demonstrated to influence the plasma carotene are (1) the diet; (2) the stability of carotene in the intestinal tract; (3) the rate and amount of carotene absorption; (4) the rate of conversion of carotene into vitamin A; (5) the rate of removal of plasma carotene by liver or tissues; (6) the possible effects of other blood constituents, e.g., proteins, lipids.

Cadman's work was directed toward determining which of these factors might be influenced by the thyroid hormone. Using spectrophotometric methods, chromatography and the Carr-Price reaction, he established values for serum carotenoids, carotene and vitamin A in the normal state and in hyperthyroid and hypothyroid states. These are summarized in table 2.

Table 2

Clinical State	No. of Cases	Carotenoids μg.% plasma		Carotene μg.% plasma		Xanthophyll μg.% plasma		Vitamin A μg.% plasma	
		Means S.D.*	Ranges	Means S.D.*	Ranges	Means S.D.*	Ranges	Means S.D.*	Ranges
Normal	61	50±17	21–94	15±7	4–31	36±11	16–78	36±11	6–68
Hyperthyroidism	13	43±19	14–85	14±7	7–37	29±14	5–52	34±11	19–62
Hypothyroidism	16	105±81	33–375	33±31	10–145	72±52	22–230	36±8	24–48

* S.D. = standard deviation.

From this it can be seen (1) that there are wide ranges in the plasma carotenoids, carotene and vitamin A levels in both normal and dysthyroid states; (2) that the normal and hyperthyroid values for carotenoids and vitamin A cover approximately the same ranges, and (3) that the standard deviations of the carotenoids in the hypothyroid are considerable, and overlap the corresponding normal values, but reach much higher maximal figures. The plasma vitamin A rises but little in hypothyroidism, so that the ratio of carotene to vitamin A increases. Moreover, although high levels of blood cholesterol and lipids were found in this series of hypothyroid patients, no clear evidence of a constant correlation between carotene, vitamin A and cholesterol was found. The two cases of myxedema which have been quoted illustrate the return to normal of plasma levels of carotene during effective treatment.

Although in the hyperthyroid group there is no significant variation from the normal range of plasma carotene, when such patients are treated and rendered euthyroid there is a trend toward higher carotene levels as the clinical condition improves.

It is not yet possible to answer with certainty the question, Does the

thyroid hormone in man facilitate the absorption of carotene or promote its conversion into vitamin A, or both? But it is highly probable that the promotion of the conversion of carotene to vitamin A by thyroid is an important element, for the following reasons:

The level of plasma carotene is the difference between the amount absorbed and the conversion of carotene to vitamin A in the wall of the gut. In hyperthyroidism the blood carotene is lowered; the work of Cama and Goodwin [2] suggests that the carotene directly absorbed is increased, thus conversion of carotene into vitamin A must be increased. Conversely, in hypothyroidism blood carotene is increased but absorption is decreased; thus conversion of carotene into vitamin A must be decreased.

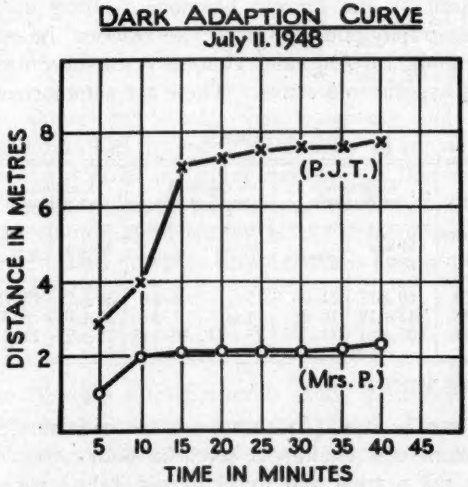

FIG. 2. Shows the dark adaptation curve of Mrs. D. P. when first seen, compared with a normal.

Cadman found also that the plasma xanthophyll levels undergo changes parallel to the plasma carotene levels, suggesting that although the xanthophylls are not provitamin A, thyroid plays a part in the destructive oxidation of the xanthophylls.

CAROTENEMIA AS AN INBORN ERROR OF METABOLISM

We have observed what is, in our experience, a unique case in which it would appear that hypercarotenemia resulting from a failure to convert carotene into vitamin A is due to an inborn error of metabolism.

Case 3. It is now nearly nine years since we first saw Mrs. D.P., then aged 38 years, who was referred as "hemolytic jaundice" or "anemia." She gave a history dating back several years of a yellow tinge of the skin and some loss of weight. There was no relevant past illness or family history, and she had taken a normal diet.

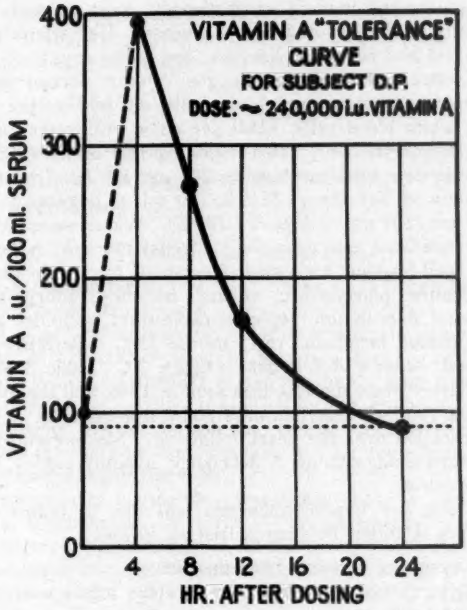

FIG. 3. Shows a normal vitamin A absorption by Mrs. D. P. after 240,000 i.u. vitamin A.

TABLE 3

Blood Analyses (Mrs. P.)

Date	Comments	Cholesterol mg./100 ml.	Vitamin A i.u./100 ml.	Carotenoids μg./100 ml.		
				Total	Carotene	Xantho-phyll
	Normal values	120–220	120–150	100	30–60	50–70
					C<X	
21-5-48	Admission	156	15	282	162	120
8-7-48	After 6 weeks of adequate vitamin A	—	100	206	135	71
13-7-48	Four samples taken	—		175 218 178 181	136	38
19-7-48	Low carotene diet started: additional vit. A, B, C, D.	—	100	140		
21-9-48	Oxalated blood Clotted blood		142 139	257 218	207 169	50 49
10-5-49		180	110	276	180	90

On examination she showed general xanthodermia, most marked in the palms and soles but also slightly in the lips and buccal mucosa. Her sclerotics were clear and her hair was lustreless and rusty and her skin dry. The results of the investigations were as follows: *Urine:* no bile or urobilinogen. *Feces:* normal stercobilin. *Blood: moderate iron deficiency anemia* (red blood cells, 4.6 million per cubic millimeter; hemoglobin, 64%; white blood cells, 4,000 per cubic millimeter; neutrophils, 2,900; lymphocytes, 800; monocytes, 240), with *histamine-fast achlorhydria.* Reticulocytes, 0.1%. *Hypercarotenemia:* total carotenoids, 282 μg./100 ml. (carotene, 162; xanthophyll, 120). *Vitamin A deficiency,* 15 i.u./100 ml. Cholesterol, 156 mg./100 ml. Total protein, 7.75 gm./100 ml. (A.G. = 1.22:1.) Wassermann reaction, completely negative. Glucose tolerance not impaired. Sternal marrow, no significant change. *X-rays* of chest, gall-bladder and gastrointestinal tract, no abnormality. *Liver function tests:* alkaline phosphatase, thymol turbidity, bilirubin, colloidal gold, zinc turbidity, thymol flocculation, cephalin cholesterol, colloidal gold and hippuric acid, all normal. *Basal metabolic rate,* minus 15%. *Defective dark adaptation* (figure 2). *Normal vitamin A tolerance* (figure 3). Table 3 shows the detailed results of blood analysis when she was first seen in 1948, and the effects on her blood carotene and vitamin A of giving vitamin A and a low carotene diet. These findings have remained unchanged over the years following. She presented clinically, therefore, with hypercarotenemia, vitamin A deficiency, hypothyroidism, an iron deficiency anemia and achlorhydria.

The evidence that her hypercarotenemia was due to failure of conversion of carotene into vitamin A might be summarized as follows:

1. Absence of excess of carotene from the diet.
2. Persistent hypercarotenemia with low carotene intake over several years.
3. Normal blood lipids.
4. Vitamin A deficiency, though absorption of vitamin A is normal.
5. Carotene content of the serum constantly greater than its xanthophyll content.

It is of interest that what appears to be primarily a hypercarotenemia is accompanied by a moderate degree of hypothyroidism, another indication of a probable reciprocal relationship between carotene and vitamin A. Moreover, as in many cases

TABLE 4

Hypercarotenemia

Probable Mechanism	Plasma Carotene	Xanthophyll: Carotene Ratio	Plasma Vitamin A	Blood Lipids
1. Excessive intake	Increased	>1	Increased	Normal
2. Hyperlipemia a. Diabetes mellitus b. Nephrotic syndromes c. Hypercholesteremic lipoidoses d. Hypothyroidism*	Increased	>1	Normal or increased	Increased
3. Failure of conversion of carotene into vitamin A				
a. Inborn error of metabolism	Increased	<1	Decreased	Normal
b. Hypothyroidism*	Increased	>1	Often increased	Increased
4. Failure of oxidation of carotene (? role of thyroid and iron)	Increased	?	Increased	Normal

* The two mechanisms brought into play in hypothyroidism are responsible for variable results.

of carotenemia, there are here an iron deficiency anemia and achlorhydria. There is some evidence to suggest that in an iron deficiency anemia there may be failure of oxidation of carotene, with resulting carotenemia.

Summary

Table 4 summarizes the conditions under which hypercarotenemia might be found clinically, and the suggested mechanisms and blood changes which help in their differentiation.

Summario in Interlingua

Le causas de xanthodermia include (1) jalnessa, (2) injection de colorantes jalne, per exemplo safran, e (3) carotinemia.

Carotinoides es de origine vegetal. Illos es incontrate in omne vegetales verde, multo concentrate in carotas, e etiam in butyro e ovos. Lor formula general es $C_{40}H_{56}O_n$ (ubi n = 0 a 6). Carotinas es hydrocarburos (con n = 0). Lor derivatos hydroxylic es xanthophyllas. Beta-carotina es le plus importante precursor de vitamina A. Normalmente, 100 ml de sanguine contine circa 100 mg de carotinoides e 120 a 150 unitates international de vitamina A. Le proportion de xanthophylla a carotina es approximativemente duo a un.

Le major recognoscite causas de carotinemia es: (1) Ingestion excessive de vegetales verde e, specialmente, de carotas—frequentemente in dietas adoptate pro reducer le peso corporee. In iste typo le nivello de carotina pote montar a supra 500 mg per 100 ml; etiam le contento de vitamina A cresce, sed le proportion de xanthophylla a carotina remane plus que 1. (2) Diabete mellite. On crede que duo factores es active in tal casos, i.e. le ingestion excessive de carotina e hyperlipemia. (3) Altere statos hyperlipemic. Istos include lipoidoses hypercholesterolemic, syndromes nephrotic, e hypothyroidismo. (4) Un error metabolic in que le conversion de carotina in vitamina A es defective. In tal casos, carentia de vitamina A accompania le presentia de excessos de carotina in le sanguine, durante que le absorption de vitamina A es normal.

Es discutite le relation inter carotina e le metabolismo thyroide.

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RESPIRATORY VIRUSES AND HEART DISEASE*

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Remarkable advances in the discovery of new viruses and in the recognition of human virus diseases have been made during the last 25 years. Despite such progress, a comprehensive appreciation of the clinical and pathologic spectra of heart disease due to viruses is still unrealized. One of the significant gaps in our knowledge concerns the role of common respiratory viruses in the pathogenesis of cardiac lesions. Medical opinion in this regard is fragmentary and contradictory. The basis for divergent views is essentially threefold: first, it is virtually impossible for the clinician to make an accurate diagnosis of influenza or other viral respiratory infections from the symptomatology alone; second, the extended time lapse between the primary infection and the appearance of cardiac manifestations results in heart involvement being regarded as an unrelated "new" disease; and finally, the laboratory diagnosis of the viral etiology of a disease has in the past been complicated, time-consuming and expensive.

The development of new technics for the isolation of viruses has provided unlimited opportunities for renewed study of the ill-defined, unsolved diseases of the heart as well as of other illnesses, and for the reëxploration of the possible relationship of viruses to these disorders. It appears timely, therefore, in this presentation to summarize current opinion regarding the role of respiratory viruses as agents of heart disease by (1) a recapitulation of recent relevant observations at the Michael Reese Hospital; (2) a brief review of the pertinent medical literature, and (3) a critique of a number of obscure affections of the heart in the light of information obtained from the above two sources.

Part I. The Michael Reese Hospital Study

Beginning in 1950, in a study which is still in progress, complement-fixation tests for viruses (and rickettsia) and cold hemagglutinins were performed on acute and convalescent serum specimens of patients admitted to the Michael Reese Hospital who presented one of the following features:

(1) congestive heart failure without a demonstrable etiologic basis for heart disease;

(2) signs or symptoms of heart disease during or following recovery from an acute infectious disease (the latter, in each of the patients com-

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prising this study, demonstrated to be clearly viral in origin, or without clinical or laboratory evidence of bacterial or rheumatic etiology);*

(3) routine electrocardiograms suggestive of myocarditis. The demonstration of a fourfold or greater rise of specific antibodies for a particular virus during the course of the illness was accepted as evidence of the etiologic relationship of that virus to the observed disease.

With the employment of such immunologic criteria, the diagnosis of heart disease due to respiratory viruses was made in 23 patients during the period from 1950 to 1956. The diagnosis of pericarditis was made in two cases,

TABLE 1

Etiology of 23 Cases of Heart Disease Due to Respiratory Viruses

Pericarditis	
Subacute (exacerbations and remissions)	
Influenza B	2
Myocarditis	
Acute	
Complete recovery	
Influenza A	1
Influenza A′	1
Psittacosis	1
Primary atypical pneumonia virus	1
Presumptive	9
Fatal	
Presumptive	2
Subacute (exacerbations and remissions)	
Complete recovery	
Influenza A and B	1
Presumptive	2
Chronic	
Influenza B (fatal)	1
Presumptive (one fatal case)	2

that of myocarditis in 21. A specific virus etiology was identified in eight cases (table 1). The remaining 15 cases were designated as *presumptive*, either because no rise in antibody titer was observed despite an initial significant titer, or because no positive viral studies were obtained despite clinical features identical to those cases where such serologic evidence was present. Two of the presumptive group died of acute myocarditis before serologic studies could be performed, but a histologic picture compatible with a virus myocarditis was present. In none of these 15 patients was another etiologic factor for heart disease demonstrable. The detailed clinical and electrocardiographic features as well as the long term follow-up of these cases have been the subject of a previous report.[1] The more important of these features are summarized in table 2; several deserve elaboration:

* In all instances, where indicated, the following tests were performed and a negative result obtained: throat cultures, antistreptolysin titers, blood cultures, bacterial agglutinations, sputum smears and cultures, lupus and heterophil antibody tests.

Virus Pericarditis: Two patients presented a clinical picture identical to that which has been designated in the literature as idiopathic pericarditis or acute nonspecific pericarditis.[2] After typical exacerbations and remissions, complete recovery occurred in one month and five months, respectively. In both a fourfold rise in antibody titer for influenza B was demonstrated. Although idiopathic pericarditis has been reported with virus infections elsewhere in the body, influenza has not previously been established as an etiologic agent. This is surprising when one considers the high reported incidence of respiratory infection preceding the development of pericarditis,[2, 3] and is probably a reflection of the infrequency with which viral complement-fixation tests are routinely performed in such cases. The factors which

TABLE 2

Major Clinical Features of Patients with Viral Myocarditis

Symptoms	% Cases
Antecedent respiratory infection	75
Dyspnea	70
Peripheral edema	48
Orthopnea	40
Retrosternal pain	30
Weakness	30
Signs	
Tachycardia	74
Systolic murmur	52
Protodiastolic gallop	44
Congestive heart failure	44
Sensitivity of digitalis	36
Diminished apical first heart sound	13
Diastolic murmur	9

determine whether the site of predilection in any given case of influenzal heart disease is primarily the myocardium or the pericardium are at present completely obscure.

Virus Myocarditis: On the basis of their clinical course, four groups were discernible among the 21 patients with myocarditis:

1. Acute fatal myocarditis (duration: days).
2. Acute myocarditis with complete recovery (duration: two weeks to two months).
3. Subacute myocarditis (exacerbations and remissions), with ultimate complete recovery (duration: two months to four years).
4. Chronic (intractable) myocarditis (death in the two observed cases after 18 and 24 months, respectively).

It is of considerable interest to note that there was one case in group III due to combined influenza A and B infection, and one case in group IV due to influenza B. The remaining four patients comprising these two groups were of presumptive viral etiology. *These two groups of cases are indicative of the fact that viruses may be a cause of irreparable myocardial damage and chronic heart disease.*

History of Antecedent Upper Respiratory Infection: It cannot be overemphasized that an interval of from one to several weeks between the occurrence of the initial infection and the appearance of signs of cardiac involvement is a consistent feature of postinfectious myocarditis. This characteristic has been previously pointed out by others,[4, 5] but has for some reason failed to make the impression upon physicians which its clinical importance warrants. In 75% of our material such a history was uncovered, often only through painstaking questioning of the patient. Frequently patients failed to volunteer such information because they saw no relation between that illness and their present heart disease, or because the preceding infection had been trivial. Careful inquiry with respect to this facet of the history led to the correct identification of several cases of "postpartal" myocarditis and "isolated" myocarditis as instances of postinfectious myocarditis.

Congestive Heart Failure: Congestive heart failure was the dominant clinical feature of all instances of protracted and chronic myocarditis. In the latter group it was irreversible. The clinical course of two of the patients with chronic myocarditis was characterized by intractable heart failure with episodes of recurrent pulmonary emboli.* Death occurred in both after illnesses of approximately two years' duration. (Permission for necropsy was denied.) Four patients with heart failure (two with acute myocarditis and two with subacute myocarditis) were examples of so-called "postpartal heart disease" following within two months of uneventful pregnancy and delivery. In one the etiology was a combined influenza A and B infection; one was due to primary atypical pneumonia virus, and two were presumptive viral cases.

An extremely valuable clue, suggesting the possibility of myocarditis in patients with congestive heart failure, was the occurrence of ectopic rhythms with relatively small doses of digitalis. This was observed in 36% of cases, the manifestations of sensitivity consisting of the development of first or second degree A-V block or bigeminy due to ventricular premature systoles. Contrary to common belief, digitalis generally proved as beneficial in its cardiotonic effect in the heart failure accompanying myocarditis as in that due to other etiologies.

Cardiac Murmurs: The presence of a systolic murmur was a rather common finding in acute or chronic myocarditis (52%). Usually the murmur was apical in location without widespread transmission. All varieties of intensity and duration were encountered. In most instances the murmur disappeared with complete recovery. In two patients with congestive heart failure and a protracted course, a prolonged diastolic rumble was present at the apex. Both disappeared with recovery of the patient. In neither of the cases was an accentuated apical first sound or opening snap present. Such a finding would doubtless be reported more frequently in postinfectious

* Similar to the clinical course described for such entities as endocardial fibroelastosis and idiopathic ventricular hypertrophy.

myocarditis if it were not part of accepted medical dictum that the label of rheumatic heart disease is put upon all cases with such murmurs, regardless of the presence of a positive history of rheumatic stigmata, or the confirmatory auscultatory signs of organic mitral stenosis mentioned above.

Electrocardiograms: No pattern characteristic of virus myocarditis was discernible. The abnormalities of contour and rhythm are summarized in tables 3 and 4. In the three cases where left heart strain was the sole

TABLE 3

Summary of Electrocardiographic Findings in Patients with Viral Myocarditis

Contour abnormalities alone	11
Contour abnormalities with arrhythmias	7
Arrhythmias only	1
Questionable contour abnormalities	1
	20*

* In three of the total of 23 cases studied, serial electrocardiograms were lacking.

abnormality of contour, restitution did not occur despite the fact that in two of these cases there was complete recovery without residual abnormal auscultatory signs, hypertension or demonstrable radiographic enlargement of any chamber. This suggests that alterations of the myocardium incident to the healing of an inflammatory process may, per se, produce a heart strain pattern.

TABLE 4

Types of Electrocardiographic Abnormalities in Patients with Viral Myocarditis

Contour Alterations		With Complete Restitution*	Arrhythmias (All Transient)	
Nonspecific S–T–T changes	5	2	1st or 2nd degree A-V block	5
Left heart strain†	3	0	Bigeminy (due to vent. prem. systoles)	2
Ischemia‡	1	1		
Subacute pericarditis	5	2	Other (auric. prem. systoles, tachycardia, or fibrillation, nodal tachycardia)	4
Combinations of above†‡	4	3		

* Primarily in the presumptive group.
† Left heart strain patterns, isolated or in combination, were not in the influenza group.
‡ Ischemia patterns seen only in three cases associated with lobar pneumonia.

SUMMARY

The major conclusions drawn in the Michael Reese Study, to the present time, may be summarized as follows:

1. Respiratory viruses, especially influenza viruses, are a cause of acute and *chronic* heart disease.

2. If it is not appreciated that an interval may supervene between the onset of heart disease and the antecedent upper respiratory disease, the

relationship between the two may be overlooked and the cardiac complications interpreted as a "new" disease.

3. Diastolic as well as systolic apical murmurs may occur during the course of a myocarditis.

4. Sensitivity to digitalis may provide a valuable clue to the presence of a myocarditis.

5. Chronic left heart strain may be an electrocardiographic residue of a healed myocarditis.

6. Cases that clinically present features compatible with "postpartal heart disease," Fiedler's myocarditis, benign idiopathic pericarditis, endocardial fibroelastosis or "idiopathic ventricular hypertrophy" may, in many instances, be due to myocardial involvement by viruses.

Part II. Review of the Literature

Influenza: Heart involvement in influenza has been recognized for a long time, but sharp differences of opinion exist among pathologists and clinicians alike as to the extent and importance of such involvement. Finland and his associates, in reviewing the literature pertaining to the pathologic changes in the myocardium in influenza, point out that the studies of Leichtenstern, Kuczynski and Wolff, Opie, Klotz and others revealed no characteristic morphologic changes in the myocardium, and that the changes that did occur were slight.[5] Lucké, Wight and Kime[6] reported that the heart was always affected in influenza, but that the myocardial changes were limited to cloudy swelling and interstitial edema. On the other hand, reports of degenerative changes in the myocardium were described by Kirch[7] in his review of the literature on the 1918 epidemic and subsequent recurrences of influenza; and Schmorl demonstrated inflammatory changes involving the heart muscle to an extent which led him to conclude that in no other infectious disease had he seen such widespread myocardial damage.[8] Roulet reported interstitial cellular infiltration and extensive acute damage to the muscle fibers following influenza, but he attributed the lesions to mixed infections rather than to the etiologic agent of influenza.[9]

There are numerous clinical descriptions of cases of epidemic influenza where evidence of myocardial damage was recognized by symptoms or by electrocardiographic changes. A variety of cardiac symptoms, such as weakness, dyspnea, angina and sudden death, have been described; as have all types of alterations of contour and rhythm in the electrocardiogram. The report by Finland and his associates[5] of two cases of acute myocarditis due to influenza A represents the only instance in the literature in which the influenza virus was isolated and identified. Nothing of significance has been added to our knowledge since their report and review of the subject. In 1950 Borden[10] reported a single case of acute myocarditis where serial hemagglutination tests during the course of the illness led to the recognition of influenza A as the etiologic agent.

Some writers have expressed the opinion that cardiac abnormalities are the most frequent complications of influenza,[11] while others [12, 13] considered them to be infrequent. It has been the general consensus of clinicians, however, that if recovery occurs it is complete. Our experience represents the first report of an established influenzal myocarditis producing intractable cardiac disability. Almost all writers have pointed out (1) the lack of correlation between the severity of the influenza and the resultant cardiac disease, and (2) the infrequency of cardiac complications during the acute stage of the disease; on the contrary, most of such complications have been reported as occurring during convalescence, and often long after apparent complete recovery from the initial infection. Finland and his associates mentioned that, in their experience, myocarditis attributable to other acute respiratory infections has similar time relations. Our experience coincides with theirs in this respect.

Primary Atypical Pneumonia: Primary atypical pneumonia is a clinical syndrome that has been under intensive study since World War II. The disease may be produced by a number of different bacterial, fungal and viral agents. Psittacosis and influenza are two such viruses, but the majority of cases are not associated with any of these agents.[14] Cold hemagglutinins and streptococcus MG agglutination have been of value in establishing the diagnosis in only a portion of the cases. Primary atypical pneumonia (PAP) virus has been isolated from patients and produces cold hemagglutination.[15] The adenoviruses (APC) have recently been shown to induce respiratory disease clinically consistent with the syndrome of "primary atypical pneumonia." [16] In none of these patients were cold hemagglutinins or agglutinins to streptococcus MG present. It is likely that there yet remain multiple etiologic agents as yet undiscovered. It is obvious that, in view of the pleomorphic etiology of this syndrome—much of which remains unsolved—it is impossible to review comprehensively or with finality the subject of the cardiac complications of the viral pneumonias.

Painton, Hicks and Hantman [17] reported, as evidence of myocardial involvement, electrocardiographic changes in 3.7% of a series of 321 cases. These changes consisted of displacement of the S-T segment, low or inverted T waves, and aberrations of A-V or I-V conduction. In some instances the electrocardiograms were identical with those seen in acute pericarditis. Lyon [18] has also described a series of virus pneumonias demonstrating similar transient electrocardiographic changes without symptoms or signs of cardiac embarrassment.

In our series of viral myocarditides [1] there were four patients with "atypical" pneumonia. One patients died with an acute myocarditis and pneumonic consolidation of both lungs. Autopsy revealed a confluent interstitial bronchopneumonia with hyaline membrane formation. A second patient developed congestive heart failure as an initial manifestation of acute myocarditis during convalescence from an acute pneumonia. A titer of cold

hemagglutinins in excess of fourfold was demonstrable during the disease. Recovery was without cardiac sequelae. The third patient developed dyspnea, gallop rhythm, disproportionate tachycardia and electrocardiographic abnormalities during the course of an atypical pneumonia in which cold agglutinins were negative. Complete recovery followed. The last patient, with a protracted (subacute) myocarditis, entered the hospital in congestive heart failure, with hepatitis, lobar pneumonia and a heterophil antibody titer of 1 : 160. Disappearance of all signs and symptoms of heart disease occurred some two months later.

Pericarditis which follows a clinical course like that described for "benign idiopathic" pericarditis has been described as following in the wake of an atypical pneumonia.[19, 20] This is not surprising in view of the fact that upper respiratory infections, varying from minor to severe, precede 40 to 66% of all reported cases of idiopathic benign pericarditis.[2, 3]

Psittacosis: Extensive summaries of the salient features of psittacosis [21, 22] contain no mention of significant pathologic lesions in the heart, or of clinical manifestations due to cardiac involvement. Dilatation of the heart, cloudy swelling, interstitial edema and interstitial infiltration of the myocardium and subendocardial hemorrhages are variously reported by a number of authors.[18] The clinical manifestations and severity of psittacosis vary within wide limits. Subclinical infections occur frequently, and mild infections often go unrecognized as common upper respiratory diseases. Psittacosis may simulate a variety of infectious diseases, such as influenza, infectious mononucleosis or rheumatic fever. It is quite possible, therefore, that many instances of myocarditis due to psittacosis also go unrecognized. Wuhrmann [4] attributed sudden death in an adult patient convalescing from psittacosis to interstitial myocarditis. In our series there was a single patient, a 31 year old female, in whom clinical and electrocardiographic evidence of acute myocarditis occurred three weeks after recovery from a "flu" syndrome. During the course of observation a fourfold rise in antibody titer for psittacosis was obtained. The patient had no pet birds, but kept chickens. Consistent with the clinical circumstances in this patient, Meyer and others have called attention to the few recognized instances of human psittacosis infections believed to have come from chickens, and to the mild nature of the clinical symptoms.[23]

Coxsackie B: Although the Coxsackie B group of viruses is generally classified as neuromyotropic viruses, reports of their association with a wide variety of clinical disorders, including acute, febrile, influenza-like illnesses, warrant their inclusion in a discussion of respiratory viruses. Patchy myocarditis has been noted in suckling and adult mice inoculated with certain Group B strains.[24–27] Recent reports [28, 29] indicate that strains of Coxsackie virus Group B, Type 3, may produce similar cardiac lesions in man. In 1956 Montgomery and his associates [30] described an acute illness involving three infants. Postmortem examination of the one fatal case revealed a

focal myocarditis. From the stools of this case and one of the surviving infants a Coxsackie virus Group B, Type 4, was recovered. In the same year Javett described a similar earlier outbreak in Johannesburg. Six of 10 babies died. All of the autopsied cases where histologic examination was performed showed myocarditis. Evidence for the presence of a Coxsackie virus Group B was obtained from two of the four surviving infants.[28] More recently an instance of prenatal infection with Coxsackie virus Group B, Type 3, was reported.[29] The infant died with a meningo-encephalitis and acute myocarditis, and the virus was recovered from the spinal cord. The above and additional current accounts of fatal myocarditis due to Coxsackie virus Group B [31, 32] indicate that, under special circumstances, these new viruses are capable of producing severe, fatal human disease.

Part III. Obscure Diseases of the Heart and Respiratory Viruses

Isolated (Fiedler's) Myocarditis: The term "isolated myocarditis" was applied by Scott and Saphir [33] to acute myocarditis, unaccompanied by endocarditis or pericarditis and unassociated with a primary disease or other *apparent* origin. The first clear account of this disease was given by Fiedler in 1899,[34] and hence it is often referred to as Fiedler's myocarditis. Histologically, the myocarditis does not vary in detail from that seen in the course of acute infections. Saphir pointed out that the usual clinical picture is one of rapidly progressive intractable heart failure or sudden death,[35] but others [36, 37] have shown that a truly chronic form exists which ultimately culminates in death. Since the early reports of this disease, evidence has continued to accumulate which indicates that hypersensitivity to a number of drugs (antisera, sulfonamides, penicillin, emetine, etc.) or virus infections is the most likely responsible factor.[38]

The case for virus infection as a frequent cause of isolated myocarditis is a strong one. Schmidt pointed out that the myocarditis produced in mice and guinea pigs with the encephalomyocarditis virus was remarkably similar to the myocardial lesions found in human heart muscle in several virus diseases and in "isolated" myocarditis.[39] This led him to suggest that Fiedler's myocarditis might be caused by a virus.

Covey,[40] in a report of a case of isolated myocarditis, concluded that the disease is a virus infection of the heart muscle. He pointed out that in 14 cases of Fiedler's myocarditis where a history of preceding infection was established, six were either influenza or acute upper respiratory infections. In the case reported by Covey, the pathologic findings in the spinal cord and lungs were compatible with a virus infection, and the changes in the myocardium itself were suggestive of the explosive cell destruction by a virus followed by an inflammatory response and ultimate fibrosis.

One of the two cases described by Finland et al.[5] from whom influenza A virus was isolated, and the case reported by Borden [10] with serologic evidence

of influenza A as the etiologic agent, had the essential characteristics of acute isolated myocarditis. The close resemblance of the myocarditis associated with Coxsackie virus, Group B to Fiedler's myocarditis was stressed by Kibrick and Benirschke.[29] Seventy-five per cent of our case material [1] would have been designated as "isolated" myocarditis if the relationship to influenza or other upper respiratory infectious agents had not been established. At the present time there seems to be little purpose served by retaining the designation "isolated myocarditis." As more is learned concerning the response of the myocardium under various conditions, the diagnosis of isolated myocarditis will become less frequent; it appears safe to venture that respiratory viruses will play a significant role in making the term obsolete.

Idiopathic Ventricular Hypertrophy: In 1901 Josserand and Gallavardin described the first recorded case of so-called "idiopathic ventricular hypertrophy." [41] Since then approximately 60 cases have been reported.[42, 43] The clinical features are identical with those of chronic myocarditis or the myocarditis perniciosa of Boikin, namely, intractable congestive heart failure, commonly mural thrombi with pulmonary and systemic emboli, and often auricular flutter or fibrillation. The predominant histologic findings were hypertrophied muscle fibers, degenerative changes in the myocardium, inconspicuous degrees of cellular infiltration, and a tendency to formation of mural thrombi. The inflammatory or toxic origin of this condition cannot be excluded because, with chronicity, myocardial fibrosis occurs regardless of whether the etiologic agent was infectious, toxic or degenerative in nature. Most of the papers written on the subject have been by pathologists who have merely abstracted clinical protocols without first-hand knowledge of the patient. Rarely in such reports is it apparent whether careful inquiry was made in each instance as to the occurrence of previous upper respiratory infection. Our experience [1] has led us to conclude that in many instances idiopathic cardiac hypertrophy is a "burned out" stage of a chronic viral myocarditis.

Endocardial Fibroelastosis: Although the condition is most often encountered in infants under one year of age, it has been reported in adults as well.[44] In the adult the clinical picture is similar to that of chronic isolated myocarditis and idiopathic ventricular hypertrophy, with heart failure and thrombo-embolic phenomena the conspicuous features. Histologic studies of such cases show massive thickening of the endocardium by fibrous tissue. Degenerative changes are also present in the myocardial fibers, even in regions of the heart that show no endocardial lesions. The etiologic relationship of viruses, toxins, ischemia or malnutrition is at present entirely speculative.

Postpartal Heart Disease: The medical literature of the last 20 years contains a number of reports which describe heart failure appearing in the last month of pregnancy or first few weeks of the puerperium in the absence

of any recognizable preëxisting cardiac lesion.[45–54] Since such cases have clinically suggested the presence of acute diffuse myocardial disease, heart failure of this type has been designated "postpartal heart disease" or "postpartal myocarditis." The myocardium in fatal cases has shown moderate infiltration, primarily by lymphocytes and macrophages.,

In none of the reported cases has any evidence been presented that pregnancy is etiologically related to such heart disease, aside from the time sequence. Affixing a label to these cases has, until recently, throttled interest in searching for specific precipitating factors. However, in 1954 Bashour and Winchell [55] reported two cases that, on the basis of circumstantial evidence, suggested sulfonamide sensitivity as the etiologic agent in one patient, and influenza A-prime virus in the other. Both patients continued to show evidence of serious heart disease after recovery from the initial bout of failure. Four of our cases of viral myocarditis were instances of postpartal myocarditis. One was due to primary atypical pneumonia virus and one to mixed influenza A and B infection. Two were of presumptive viral origin. All have ultimately been restored to a normal functional capacity, with normal heart size, but there has not been complete restitution of the electrocardiograms to normal.[1] Benchimol and Schlesinger in their study were impressed with the possibility of obstetric hemorrhage and inadequate diet during pregnancy as being of etiologic importance.[56] From the preceding evidence it would appear that diffuse myocardial disease in the puerperium is related to a number of different etiologic agents, and that there is no real evidence to warrant the designation of postpartal heart disease as a separate entity.

Summary

The clinical features of 21 cases of myocarditis and two cases of pericarditis have been presented in which the diagnosis of viral etiology was established by serologic tests, or exclusion of other recognized etiologies. The latter group was designated as presumptive. Actually, it should be pointed out that, in the final analysis, the appearance of antibodies for a virus during the course of a disease does not in itself constitute incontrovertible proof that the virus is responsible for the malady, although it is highly suggestive evidence. Neither does the isolation of a virus having a temporal relation to a disease process of itself prove that this represents the etiologic agent. Finland and his associates [5] pointed this out clearly in discussing the recovery of influenza A from the lungs of their two cases of fatal myocarditis. The application of "Rivers' Postulates in Viral Diseases" [57] can seldom be fulfilled in human myocarditis. Human autopsy tissue for histologic and etiologic studies is seldom available; tissue from biopsy, even more rarely. Moreover, few viruses produce morphologic lesions that are diagnostic, nor does it appear necessary to assume that a virus must actually be present in the tissues of the heart to induce myocardial lesions. These

are only a few of the factors in the "virologist's dilemma" [57] in establishing an etiologic relationship between prevalent viruses and prevalent diseases.

Although the viral etiology of our cases of myocarditis must therefore be considered *sub judice,* the purpose of this paper will be served if it renews clinicians' interest in this problem. The only method by which this type of heart disease can be viewed in its proper perspective is by careful follow-up studies encompassing many years. This type of research, as has been pointed out,[58] does not require elaborate equipment: "It can and will probably be best carried on by the practising physician, because he is in the best position to see patients when they are in the acute stages of common infectious diseases, and to arrange for and carry out the long-term study by means of which important contributions to our knowledge will be made."

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SUMMARIO IN INTERLINGUA

Super le base del studio de 21 casos de myocarditis e de duo casos de pericarditis, datos es presentate in supporto del these que virus e specialmente virus de influenza es un causa de acute e mesmo de chronic morbo cardiac. Le agente causal esseva identificate per le demonstration de anticorpore specific pro virus de influenza o psittacosis o del presentia de cryoagglutininas. Es signalate le facto que le relation inter un antecedente infection supero-respiratori e le subsequente myocarditis es communmente ignorate a causa del prolongate intervallo de tempore que separa le duo. Altere importante aspectos clinic que es notate include le sequente: Murmures diastolic e etiam systolic pote esser presente supra le precordio durante le curso de un myocarditis. Sensibilitate a digitalis pote provider un importante indice quanto al presentia de un myocarditis. Il non existe un specific configuration electrocardiographic pro myocarditis virusal. Chronic tension sinistro-cardiac es possibilemente un residuo electrocardiographic de un resanate myocarditis.

Es presentate un breve revista del litteratura summarisante le rolo del bencognoscite typos de virus respiratori (influenza, psittacosis) e de certes del plus recentemente discoperite typos (primari pneumonia atypic, adenovirus, virus Coxsackie). Le relation inter istos e obscur affectiones del corde es explorate.

Es concludite que casos presentante clinicamente characteristicas compatibile con "morbo cardiac post parto," myocarditis de Fiedler, benigne pericarditis idiopathic, fibroelastosis endocardial, o idiopathic hypertrophia ventricular es partialmente causate per un affection virusal del myocardio.

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FUNGAL ENDOCARDITIS: REVIEW OF THE LITERATURE AND REPORT OF THREE CASES*

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INTRODUCTION

ENDOCARDIAL involvement in fungal disease is uncommon. Its true incidence has been obscured by confusion in terminology by both clinicians and bacteriologists. According to commonly accepted methods of classification,[1, 2] the higher fungi (*Eumycetes*) are separated from the bacteria (*Schizomycetes*). To the latter category belong not only the common bacteria but also the so-called higher bacteria, including, among others, the following organisms which have been implicated in endocarditis:[3-5] *Actinomyces bovis, Actinomyces graminis, Actinomyces septicus, Nocardia asteroides, Leptothrix, Streptobacillus moniliformis* (which is also called *Streptothrix* and *Actinomyces muris*), *Erysipelothrix rhusiopathiae,* diphtheroids, *Listeria monocytogenes,* and *Actinobacillus lignieresi.* Since none of these organisms belongs to the *Eumycetes,* they will not be included in the following discussion, and the term "fungus" will be used to connote the *Eumycetes.*

Among the fungi, those reported as the etiologic agent in endocarditis include: *Coccidioides immitis, Cryptococcus neoformans, Blastomyces dermatitidis, Histoplasma capsulatum,* several species of *Candida* and *Aspergillus,* and one species of *Mucor.* A total of 31 adequately documented cases of fungal endocarditis have been reported previously.[4, 6-32] These are listed in tables 1A and 1B. In addition, several other cases have been reported[33-40] which we feel lack sufficient evidence of specific fungal endocarditis for inclusion in this review. These cases and the reasons for their exclusion are listed in table 2. The occurrence of *Candida parakrusei* on the surface of a left atrial myxoma, associated with *Candida fungemia,* has recently been reported by Dick and Mullin.[41] This probably cannot be considered an example of endocarditis.

To the 31 acceptable cases previously noted, the present report adds three additional cases: two due to *Histoplasma capsulatum* and one due to

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Coccidioides immitis. In the following discussion the cases presented in tables 1A and 1B are separated according to the exact etiologic agent involved, and each group is analyzed briefly. Our own three cases are included and are presented in detail.

Candidiasis

Eleven adequately documented cases of candida endocarditis are summarized in the accompanying table. Nearly all presented many of the classic physical and laboratory findings usually associated with bacterial endocarditis. One feature that occurred with impressive frequency in this group, however, was embolism to the large arteries, which often was a presenting manifestation, or one which directed attention to endocarditis as a diagnostic possibility. The frequent occurrence of such major arterial emboli appears to be related to the large size that mycotic vegetations may assume. In six of these 11 cases, the vegetations were 1.5 cm. or more in diameter. Some others were described as large, but measurements were not given. Two patients (cases 6 and 7) of the 11 with candida endocarditis had no evidence of preëxisting valvular heart disease. The others (cases 1 through 5 and 8 through 11) had probable or definite evidence of previous valvular damage.

In contrast to most other types of mycotic endocarditis, the diagnosis of candida endocarditis was frequently made during life, presumably because of the ease with which candida can be isolated from the blood, using ordinary culture media. Candida endocarditis frequently appeared to be the result of initial implantation of the organism on the heart valves, with subsequent hematogenous dissemination, rather than a manifestation of an already widely disseminated fungal infection.

In seven cases (cases 1, 2, 4, 5 and 11, and two cases mentioned briefly by Wikler et al.[7]), a probable portal of entry of candida organisms into the blood stream was present. Five of these patients were narcotic addicts who employed unsterile procedures in intravenous injection of narcotics. One patient (case 4) had received prolonged intravenous penicillin therapy preceding the candida endocarditis, and one (case 11) may have had the organism implanted directly during aortic valvulotomy. No obvious portal of entry was noted in the remaining cases.

In addition to a likely portal of entry, antibiotic therapy might be considered to be a factor predisposing to candida endocarditis, as has been suggested for other severe candida infections.[10, 42] In the three patients who received antibiotics (cases 4, 10 and 11), these drugs may have played such a role. However, in the remaining cases it appeared more likely that other factors, namely, the aforementioned portal of entry and preëxisting valvular damage, were of greater importance.

TABLE 1A

Clinical Manifestations of Fungal Endocarditis

Case No.	Author	Organism	Age	Sex	Presenting Manifestation	Physical Findings							Associated Disease	Pertinent Drug Therapy (before onset)	Total Duration (from probable onset)	Clinical Diagnosis
						Heart Murmur	Fever	Petechiae	Splenomegaly	Hepatomegaly	Evidence of Major Emboli* to:	Other				
1.	Joachim, Polayes[6]	*Candida parakrusei*	48	M	Abdominal pain	+	+	+	+	+	Skin	..	Narcotic addiction	None	5 mos. (?)	Candida endocarditis
2.	Wikler, Williams, Douglass, Emmons[7]	*C. parakrusei*	49	M	Hemiplegia	+	+	+	+	..	Brain	..	Narcotic addiction	None	3 mos.	Candida endocarditis
3.	Pasternack[8]	*C. parakrusei*	45	M	Abdominal pain, fever	+	+	+	+	+	Ileum	..	None	None	36 days	Candida endocarditis
4.	Geiger, Wenner, Axilrod, Durlacher[9]	*C. albicans*	18	F	Meningeal signs, fever, Osler's node	+	+	+	..	..	Skin, brain, spleen, kidney	Meningeal signs	Previous bacterial endocarditis	Penicillin I.V.	16 days	Candida endocarditis
5.	Zimmerman #1[10]	*C. guilliermondi*	38	F	Abdominal pain, fever	+	+	+	..	..	Mesenteric artery	..	Narcotic addiction	None	1 mo.	Not stated
6.	Wolfe, Henderson[11]	*C. krusei*	57	F	Fever, cough	+	+	+	+	+	Leg	..	Diabetes mellitus, pyelonephritis	None (?)	3 mos.	Pyelonephritis, chronic
7.	Kunstadter, MacLean, Greengard[12]	*C. albicans*	7 mos.	M	Fever, cough	..	+	+	+	+	–	Pneumonitis, thrush	Chronic respiratory illness	Sulfonamides (?)	1–2½ mos.	*Candida fungemia*
8.	Niel and Kohlmeier #1[12a,b]	*C. albicans*	41	M	Increasing heart failure	+	+	..	+	–	–	..	None	None	2 mos.	Candida endocarditis
9.	Niel and Kohlmeier #2[12a,b]	*C. guilliermondi*	59	F	Fever, heart failure	+	+	..	+	+	–	..	Hypertension	None	3 mos.	Candida endocarditis
10.	Caplan[14]	Candida	43	M	Embolus to leg	+	+	+	..	..	Brain, leg	..	Perforated peptic ulcer (gastrectomy)	Many antibiotics	1 mo. (?)	Not stated
11.	Koelle, Pastor[15]	*C. albicans*	40	M	Fever, chest and abdominal pain	+	+	+?	+	+	Brain, leg, skin, kidney, mesenteric artery	..	(Aortic valvulotomy)	Penicillin Streptomycin	12+ days	Candida endocarditis

TABLE 1A—*Continued*

Case No.	Author	Organism	Age	Sex	Presenting Manifestation	Physical Findings							Associated Disease	Pertinent Drug Therapy (before onset)	Total Duration (from probable onset)	Clinical Diagnosis
						Heart Murmur	Fever	Petechiae	Splenomegaly	Hepatomegaly	Evidence of Major Emboli* to:	Other				
12.	Hurley[16]	*Blastomyces dermatitidis*	61	M	Cough, dyspnea	..	..	−	−	−	−	−	None	None	10 mos.	Not stated
13.	Baker, #1 Brian[17a]	*B. dermatitidis*	17	M	Subcutaneous abscess	−	+	−	−	−	−	Heart failure	None	None	24 mos.	Blastomycosis
14.	Baker, #2 Brian[17a]	*B. dermatitidis*	24	M	Subcutaneous abscess	+	+	−	−	−	−	Heart failure	None	None	13 mos.	Blastomycosis
15.	Pond, Humphreys[18]	*B. dermatitidis*	17	M	Embolus to leg	+	+	−	−	−	Leg	−	None	None	2 wks.	Bacterial endocarditis
16.	Epstein[19]	*Coccidioides immitis*	..	..	..	..	..	..	..	..	..	..	..	..	..	Coccidioidomycosis
17.	Present authors	*C. immitis*	21	M	Subcutaneous abscesses	+	+	?	−	+	−	Heart failure	None	None	11 wks. (?)	Coccidioidal myocarditis and pericarditis
18.	Cawley[20]	*Aspergillus fumigatus*	8	M	Cerebellar signs	..	..	..	..	..	?Cerebellum	Cerebellar signs, pneumonia	None	Sulfonamides	6 mos. (?)	Aspergillosis, generalized
19.	Zimmerman #2[10]	Aspergillus	25	M	Fever, embolus to leg	+	+	..	+	..	Leg	..	Septic amputation site	Penicillin	2 wks.	Bacterial endocarditis?
20.	Welsh, Buchness[21]	*A. flavus*	18	M	Fever	..	+	..	−	..	−	..	"Splenic neutropenia," interstitial pneumonia	Corticotropin Cortisone Antibiotics	1 mo.	"Collagen disease"
21.	Kirschstein, Sidransky[22]	*A. flavus*	50	M	Fever, weakness	..	+	..	+	+	−	..	Chronic lymphocytic leukemia??	Corticotropin Antibiotics	1 mo. (?)	Chronic lymphocytic leukemia
22.	Lombardo, Rabson, Dodge[23]	*Cryptococcus neoformans*	44	M	Increasing heart failure, headache	+	+	+	+	+	Skin, ?Myocardium	Heart failure	None	None	8½ mos.	Cryptococcal endocarditis
23.	Broders, Dochat, Herrell, Vaughn[24]	*Histoplasma capsulatum*	47	M	Fever, malaise	+	+	−	+	+	−	..	None	None	7 mos.	Histoplasmosis

TABLE 1A—*Continued*

Case No.	Author	Organism	Age	Sex	Presenting Manifestation	Physical Findings							Associated Disease	Pertinent Drug Therapy (before onset)	Total Duration (from probable onset)	Clinical Diagnosis
						Heart Murmur	Fever	Petechiae	Splenomegaly	Hepatomegaly	Evidence of Major Emboli* to:	Other				
24.	Kemper, Bloom[25]	*H. capsulatum*	59	M	Ulcer on tongue, weakness	−	+	−	−	−	−	Heart failure	None	None	10 mos.	Not stated
25.	Parsons, Zarafonetis Case E[26]	*H. capsulatum*	60	M	Sore tongue	−	+	−	−	−	−	Pneumonitis	None	None	8 mos.	Not stated
26.	Beamer, Reinhard, Goodof[4]	*H. capsulatum*	54	M	Chills, fever, lethargy	+	+	−	−	−	−	Cardiomegaly, tabes dorsalis	Tertiary syphilis	None	7½ mos.	Syphilis
27.	Fawell, Browns, Ernstene[27]	*H. capsulatum*	55	F	Fever, cough, weakness	+	+	−	+	−	−	Cardiomegaly	None	None	5 mos.	Not stated
28.	Binford† Zimmerman[28a,b] #3[10,29]	*H. capsulatum*	32	F	Fever, nausea	+	+	+	+?	+	Legs, spleen	..	None	None	13 mos.	Bacterial endocarditis
29.	Binford‡[28a,b] Sulack[30]	*H. capsulatum*	64	M	Incoordination, weakness	−	+	−	+	+	−	Hemiparesis, ulcer in mouth	Addison's disease	None	34 mos.	Histoplasmosis
30.	Binford§[28a,b]	*H. capsulatum*	39	M	Hoarseness, weight loss, headache	+	+	+	+	+	Skin	Heart failure	Tuberculosis Candidiasis?	None	8 mos.	Histoplasmosis, myocarditis
31.	Moore[31]	*H. capsulatum*	53	M	..	..	..	..	..	..	..	..	..	..	..	..
32.	Present authors	*H. capsulatum*	56	M	Mouth ulcers, fever, weight loss	−	+	−	−	+	−	Ulcers of mouth, pharynx, larynx	Addison's disease	None	31 mos.	Histoplasmosis
33.	Present authors	*H. capsulatum*	35	M	Fever, heart murmurs	+	+	+?	+	+	−	Coarctation or aorta	Coarctation of aorta	None	21 mos.	Histoplasmosis, endocarditis?
34.	Torack[32]	Mucor	64	M	Epigastric pain, vomiting	..	..	..	+	+	..	..	Multiple myeloma	Antibiotics Corticosteroids	?	Multiple myeloma

* Includes Osler's nodes. † AFIP Acc. No. 204556. ‡ AFIP Acc. No. 173364. § AFIP Acc. No. 147816.

TABLE 1B

Clinical and Anatomical Pathology in Fungal Endocarditis

Case No.	Author	Organism	Urine	Total Leukocyte Count (per cu. mm.)	Anemia	Erythrocyte Sedimentation Rate	Blood Culture	Location of Vegetation (or endocardial lesion)	Fungus Identified Microscopically in Vegetation	Culture of Vegetation (for fungi)	Previous Valvular Damage	Other Cardiac Pathology	Major Emboli to:
1.	Joachim, Polayes[6]	*Candida parakrusei*	Casts, RBC+WBC	6,750 to 10,600	Yes	Elevated	Positive	Aortic valve	Yes	Positive	Probable	Myocarditis, pericarditis	Mesenteric A. Spleen, kidney
2.	Wikler, Williams, Douglass, Emmons[7]	*C. parakrusei*	Protein 3+ RBC "Yeast"	7,000 to 26,700	Yes	..	Positive	Mitral valve	Yes	..	Yes	Myocarditis	Brain Spleen Kidney
3.	Pasternack[8]	*C. parakrusei*	..	4,500 to 7,750	Yes	..	Positive	Aortic valve	Yes	Positive	Probable	Myocarditis	Ileum Spleen Kidney
4.	Geiger, Wenner, Axilrod, Durlacher[9]	*C. albicans*	"Yeast"	13,250	..	..	Positive	Mitral valve, left atrium	Yes	Positive	Yes	Focal myocardial necrosis	Brain
5.	Zimmerman #1[10]	*C. guilliermondi*	..	..	..	..	Positive	Mitral valve	Yes	..	Yes	..	Mesenteric A. Spleen Kidneys
6.	Wolfe, Henderson[11]	*C. krusei*	Protein RBC+WBC "Yeast"	Normal	Yes	Elevated	Positive	Mitral valve, left atrium	Yes	..	None described	Myocarditis	Spleen
7.	Kunstadter, MacLean, Greengard[12]	*C. albicans*	Protein 3+	15,500 to 56,000	Yes	..	Positive	Mitral valve	Yes	..	None described	Myocarditis, myocardial abscess	Liver, myocardium
8.	Niel, Kohlmeier #1[13a,b]	*C. albicans*	Protein Casts RBC+WBC	4,150	Yes	Elevated	Positive	Mitral and aortic valves	Yes	Positive	Probable	Myocarditis	Brain
9.	Niel, Kohlmeier #2[13a,b]	*C. albicans*	Protein Casts, WBC	12,900	No	Elevated	Positive	Mitral and aortic valves	Yes	Positive	Probable	..	Spleen
10.	Caplan[14]	Candida	RBC	..	..	..	..	Mitral valve	Yes	..	Yes	..	Brain Ext. iliac arteries
11.	Koelle, Pastor[15]	*C. albicans*	..	..	..	..	Positive	Aortic valve	Yes	Positive	Yes	Emboli to myocardium	Brain Kidney Bowel Pancreas Iliac A.

TABLE 1B—*Continued*

Case No.	Author	Organism	Urine	Total Leukocyte Count (per cu. mm.)	Anemia	Erythrocyte Sedimentation Rate	Blood Culture	Location of Vegetation (or endocardial lesion)	Fungus Identified Microscopically in Vegetation	Culture of Vegetation (for fungi)	Previous Valvular Damage	Other Cardiac Pathology	Major Emboli to:
12.	Hurley[16]	*Blastomyces dermatitidis*	..	..	..	..	..	Right atrium	Yes	..	None described	Myocarditis, pericarditis	..
13.	Baker, Brian #1[17a]	*B. dermatitidis*	Normal	8,300 to 33,000	Yes	..	..	Right atrium	Yes	..	None described	Pericarditis	..
14.	Baker, Brian #2[17a]	*B. dermatitidis*	Protein 2+ WBC+Yeast	14,200	Yes	Elevated	..	Right atrium	Yes	..	None described	Pericarditis, myocarditis	..
15.	Pond, Humphreys[18]	*B. dermatitidis*	WBC	17,000	Yes	Elevated	Negative	Left atrium	Yes	..	None described	Pericarditis, myocarditis	Kidneys
16.	Epstein[19]	*Coccidioides immitis*	..	..	..	..	Positive	"Heart valves"	Yes	..	..	..	..
17.	Present Authors	*C. immitis*	Normal	12,700	Yes	Elevated	Positive	Left atrium	Yes	..	None	Pericarditis, myocarditis	None
18.	Cawley[20]	*Aspergillus fumigatus*	..	..	..	..	..	Left ventricle	Yes	..	None described	Myocardial abscess	?Brain Spleen Kidneys
19.	Zimmerman #2[10]	Aspergillus	..	..	..	..	Negative	Aortic and tricuspid valves	Yes	..	None described	Myocarditis	Kidneys
20.	Welsh, Buchness[21]	*A. flavus*	..	1,100 to 3,500	..	..	Negative	Right ventricle	Yes	Positive	None described	None described	..
21.	Kirschstein, Sidransky[22]	*A. flavus*	Normal	850	Yes	Elevated	..	Tricuspid valve	Yes	Positive	None described	Myocarditis	Lungs
22.	Lombardo, Rabson, Dodge[23]	*Cryptococcus neoformans*	WBC	5,200	Yes	Elevated	Positive	Aortic and mitral valve	Yes	Positive	Yes	Focal myocardial necrosis, infarction	Myocardium Kidney ?Brain
23.	Broders, Dochat, Herrell, Vaughn[24]	*Histoplasma capsulatum*	Casts Protein RBC	6,900	Yes	Elevated	Negative	Mitral and aortic valves	Yes	..	Yes	None described	Spleen
24.	Kemper, Bloom[25]	*H. capsulatum*	..	6,200	Yes	Elevated	Negative	Tricuspid valve	Yes	..	None described	None described	None
25.	Parsons, Zarafonetis Case E[26]	*H. capsulatum*	Protein RBC+WBC	4,050 to 9,800	Yes	..	..	Tricuspid valve	Yes	Negative	None described	None described	None

TABLE 1B—*Continued*

Case No.	Author	Organism	Urine	Total Leukocyte Count (per cu. mm.)	Anemia	Erythrocyte Sedimentation Rate	Blood Culture	Location of Vegetation (or endocardial lesion)	Fungus Identified Microscopically in Vegetation	Culture of Vegetation (for fungi)	Previous Valvular Damage	Other Cardiac Pathology	Major Emboli to:
26.	Beamer, Reinhard, Goodof[4]	*H. capsulatum*	Protein Casts RBC	3,500 to 7,000	No	..	Negative	Aortic valve	Yes	..	Yes	None described	None
27.	Fawell, Browns, Ernstene[37]	*H. capsulatum*	Protein RBC	15,400	No	Normal	Negative	Mitral valve	Yes	Negative	Yes	None described	Spleen Kidney
28.	Binford,†[28a,b] Zimmerman #3[10,39]	*H. capsulatum*	Protein WBC	9,900	Yes	Elevated	Negative	Aortic valve	Yes	Negative	Yes	Myocarditis	Spleen Kidneys
29.	Binford,†[28a,b] Sulack[39]	*H. capsulatum*	Protein RBC	8,200	No	Elevated	..	Tricuspid valve	Yes	Positive	None described	None described	None
30.	Binford§[28a,b]	*H. capsulatum*	Protein 3+ Casts "Yeast"	7,000 to 10,000	Yes	Elevated	Negative	Aortic valve	Yes	Negative	None described	(Mycotic aneurysm of aorta)	None
31.	Moore[21]	*H. capsulatum*	..	..	..	..	..	Aortic valve	Yes	..	..	..	..
32.	Present Authors	*H. capsulatum*	RBC+WBC	11,200	No	Elevated	Negative	Aortic valve	Yes	..	None	None	None
33.	Present Authors	*H. capsulatum*	Casts WBC+RBC	7,500	Yes	Elevated	Negative	Aortic valve	Yes	Positive	None	None	None
34.	Torack[22]	Mucor	..	4,100 to 8,700	Yes	..	..	Left atrium Left ventricle	Yes	..	..	Mycotic coronary thrombus +infarct	..

† AFIP Acc. No. 204556.
‡ AFIP Acc. No. 173364.
§ AFIP Acc. No. 147816.

TABLE 2

Previously Reported Cases Lacking Sufficient Evidence of Fungal Endocarditis for Inclusion in Present Review

Author	Organism Implicated	Reason for Exclusion
Lewison and Jackson[33]	*Blastomyces dermatitidis*	Microscopic appearance of vegetation not reported
Friedman and Donaldson[34]	Yeast (Candida?)	Microscopic description of fungus inadequate for identification. No culture
Humphrey[35]	*Histoplasma capsulatum*	Microscopic appearance of vegetation not reported
Sacks and Ata[36]	*Candida albicans*	Microscopic appearance of vegetation not reported
Cassels and Steiner[37]	Candida	Culture and microscopic description inadequate for identification
Luttgens[38]	Candida	Microscopic description of fungus inadequate for identification. No culture
Zimmerman Case #3[10]	Aspergillus	Fungus subsequently identified as *H. capsulatum*[39]: case 28 (Table 1A and B)
Peeler and Riley[39]	*C. albicans*	Fungi not seen in vegetation microscopically
Paplanus and Cate[40]	Candida	Report not published. Case mentioned briefly by Peeler and Riley[39]

BLASTOMYCOSIS

Four cases of endocardial involvement by *Blastomyces dermatitidis* have been reported. In none of these was the diagnosis established ante mortem. In all four there was direct extension to the endocardium from a pulmonary or mediastinal blastomycotic lesion. In cases 12, 13 and 14 the patients had obvious blastomycosis in other parts of the body and had progressive downhill courses. The only clinical indication of cardiac involvement in these patients was the development of congestive heart failure in two. In the third a "cardiac disturbance" was reported but was not further elucidated. Thus, in these three cases, clinically apparent disseminated blastomycosis was present and overshadowed the late-appearing cardiac manifestations.

In the fourth (case 15) the first manifestation was embolism to the right leg. Fever, anemia and a changing precordial systolic murmur were present. Although five blood cultures (on blood agar incubated at 37° C.) were negative, it was felt that the most likely diagnosis was subacute bacterial endocarditis. At postmortem examination, a previously unrecognized blastomycotic lesion in the left lung was found which had penetrated the left auricular appendage to involve the left atrial endocardium. The mycelial and spore stages of the fungus were seen in the vegetation, as well as in emboli to the kidneys and meninges. In this patient the primary clinical manifestations were related to the cardiac involvement, although, as in the other three cases, this was secondary to adjacent thoracic blastomycosis which had spread by contiguity.

Coccidioidomycosis

Aside from Epstein's [19] incompletely described patient (case 16) with *Coccidioides immitis* endocarditis, no documented cases of coccidioidal endocarditis were found in the literature. In the following case, disseminated coccidioidomycosis was associated with pericardial, myocardial and endocardial coccidioidal lesions.

Case Report

Case 17. A 21 year old Negro from California was admitted to the Clinical Center November 11, 1955, with a diagnosis of disseminated coccidioidomycosis. One year prior to admission he had developed a peridental abscess which drained spontaneously. Thereafter he had severe shaking chills, sweats, and fever to 105° F. orally. A left lung lesion was found on roentgen examination, and he was hospitalized. Extensive studies for tuberculosis were negative. Two months after hospitalization a subcutaneous abscess developed in the neck and was incised. *C. immitis* was found in the necrotic material on both microscopic examination and culture. Subsequently he developed many abscesses over his trunk and extremities and was transferred to the Clinical Center for further study.

Physical examination revealed an emaciated, severely ill male with multiple subcutaneous abscesses located on his neck, chest, back, buttocks and thighs. His temperature was 38.1° C.; blood pressure, 110/70 mm. Hg; respiration, 14 per minute; heart rate, 60 per minute. The breath sounds were harsh over the left upper lobe, but there were no other pulmonary abnormalities. Examination of the heart revealed no cardiomegaly. The pulmonic second sound was louder than the aortic second sound, and there was a soft, scratchy, early and mid-systolic sound in the pulmonic area. Moderate hepatomegaly was noted, but no splenomegaly. No petechiae or Osler's nodes were present.

Laboratory examinations revealed a hemoglobin of 10.4 gm. per 100 c.c.; hematocrit, 35%; leukocyte count, 12,700 per cubic millimeter, with a differential count of 88% polymorphonuclear leukocytes, 8% lymphocytes, 3% monocytes and 1% eosinophils. The erythrocyte sedimentation rate (Westergren method) was 27 mm. per hour. Urinalysis was normal. The serum albumin was 2.7 and globulin 4.7 gm. per 100 c.c. Alkaline phosphatase was elevated at 3.4 Bessey-Lowry units. Liver function tests, blood urea nitrogen and serum electrolytes were within normal limits. Cultures of pus from subcutaneous abscesses were positive for *C. immitis*.

Over a 10-month period the patient had a progressive downhill course with many complications. These included severe anemia, bilateral pneumothoraces and severe hypoglycemia. Only the course pertaining to the cardiac manifestations will be discussed in detail.

No change was noted in the cardiac findings until January 10, 1956. At this time a soft, early systolic murmur was heard at the apex and left sternal border and was thought to be related to fever and anemia. The electrocardiogram was normal. On February 17, 1956, massive edema and ascites developed, which were considered to be manifestations of hepatic dysfunction and hypoproteinemia rather than of cardiac decompensation. On May 18 cardiomegaly was noted, and on May 22 retrosternal dullness appeared. The heart was enlarged to the right and left of the sternum, and the point of maximal impulse had shifted to the second left intercostal space. No friction rub was heard, and the heart sounds were of good intensity. There was no neck vein distention or râles, and there was no dullness paravertebrally or below the left scapula.

A chest x-ray film revealed an increase of 2.5 cm. in the transverse diameter

of the heart. Fluoroscopy showed good cardiac pulsations and no definite evidence of pericardial effusion. An electrocardiogram was unchanged. Gradually the cardiomegaly and retrosternal dullness decreased but did not disappear completely.

On June 28 nontender macules, which blanched on pressure and measured 2 to 5 mm. in diameter, appeared on the patient's hands. Over the next 10 days he developed frank congestive heart failure with râles to the midscapulae, dyspnea, orthopnea, tachypnea and cyanosis. On a therapeutic regimen which included mercurial diuretics, digitalis, low sodium diet and fluid restriction, these signs and

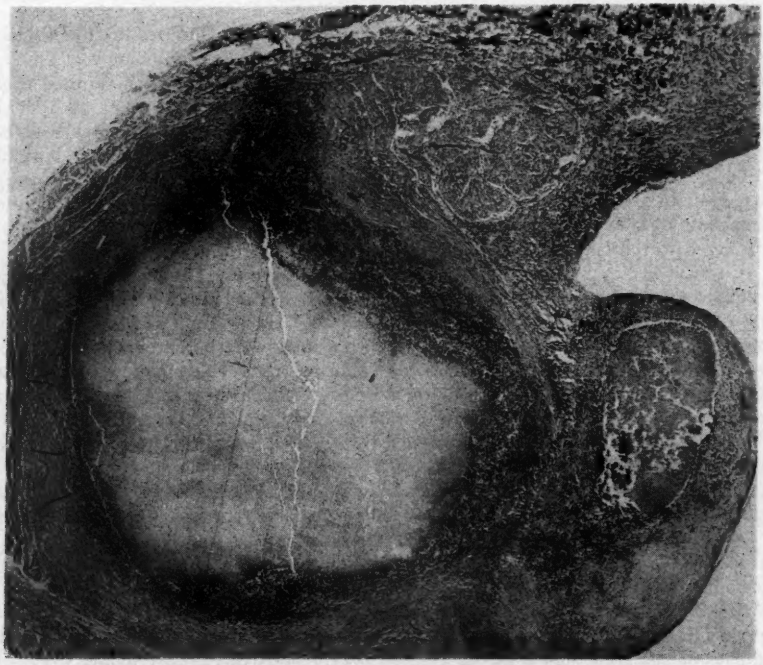

FIG. 1. *Case 17.* Coccidioidal abscess in base of mitral valve, × 15, hematoxylin and eosin.

symptoms partially subsided. Blood cultures were done for fungi and bacteria, and these remained sterile. At this time the clinical impression was myocarditis and pericarditis due to *C. immitis,* with related congestive heart failure.

On July 10, five weeks prior to the patient's death, the erythematous spots on the palms and soles appeared in increasing numbers and became papular. Some of them were slightly tender; all blanched on pressure. A biopsy examination of one such lesion revealed no specific pathologic change microscopically, and the tissue was negative on culture for fungi. Ten blood cultures for fungi and bacteria were taken and all were negative.

The patient developed pneumonitis and several pneumothoraces, so that it became difficult to determine to what extent congestive failure contributed to his dyspnea and orthopnea. No change was noted in cardiac size, the murmurs or the heart sounds, except that intermittently a protodiastolic gallop was heard to the left of the sternum. New skin lesions continued to appear. Minute vesicles were present on several of

these papules. Some hemorrhagic lesions appeared on the legs, and an exudate appeared on the retina of the left eye. A few days before death a blood culture (10 c.c. of blood in a large flask with Sabouraud's agar) was positive for *C. immitis*.

On August 4, 1956, the patient died. The clinical diagnosis was generalized coccidioidomycosis with pericardial and myocardial coccidioidomycosis. Prior to death the possibility of endocardial involvement was considered, but it was thought that the lesions on the palms and soles did not represent embolic phenomena, and the diagnosis of endocarditis due to *C. immitis* was not made ante mortem.

Postmortem Findings: At necropsy there was generalized coccidioidomycosis. There were multiple cutaneous sinuses, and over the anterior and posterior chest

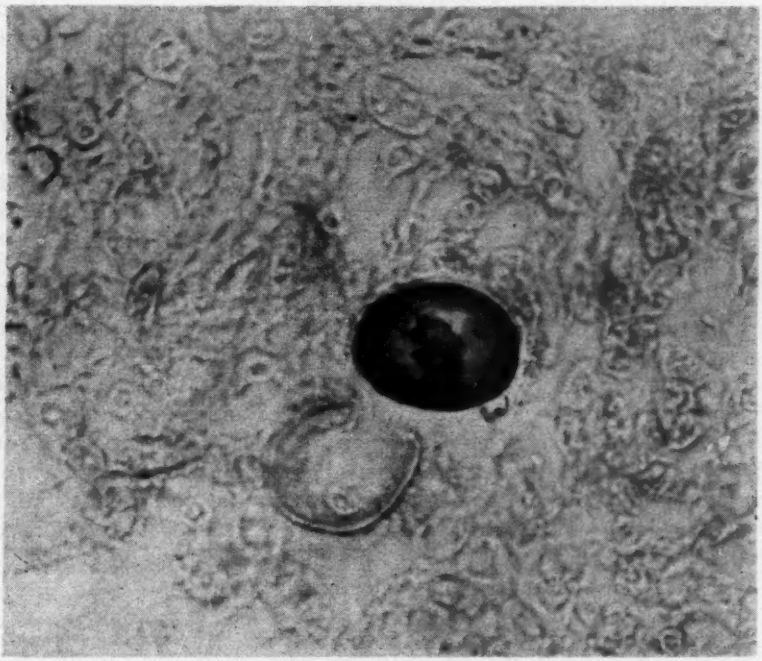

FIG. 2. *Case 17.* Spherule of *C. immitis* in abscess at base of mitral valve, × 950, Gomori methenamine silver reaction.

three pleurocutaneous fistulae. Numerous miliary granulomas were present throughout both lungs. In many areas these had become confluent. In sections of the lungs there were many areas of microabscess formation. Fibrocaseous granulomas and microabscesses were seen in the hilar lymph nodes. Endospore-filled spherules of *C. immitis* were found in both types of lesion.

The heart showed involvement of endocardium, myocardium and epicardium by *C. immitis*. Organisms were seen in the epicardium accompanied by a chronic adhesive pericarditis. There was a coccidioidal abscess measuring 1 cm. in diameter in the base of the mitral valve involving both the myocardium and endocardium of the left atrium. Histologically, this lesion consisted of an outer fibrous layer, a middle layer of organisms, giant cells, granulocytes and histiocytes, and a large central

area of caseous necrotic material (figures 1 and 2). A similar abscess was present in the adventitia of the ascending aorta near the aortic valve ring.

Coccidioidal granulomas and microabscesses were also found in the mediastinal lymph nodes, liver, spleen, pancreas, kidneys, thyroid gland, adrenal glands, prostate gland, left testis, bone marrow, skeletal muscle, meninges, pituitary gland, and in the gray and white matter of the brain.

Aspergillosis

Only four cases of aspergillosis involving the endocardium were found in the literature. In case 18 of generalized aspergillosis the endocardium was perforated by large mycotic abscesses of the left ventricular myocardium, presumably the result of hematogenous dissemination from foci of chronic pulmonary aspergillosis.

The remaining three cases (cases 19, 20 and 21) differed from the above in that the endocardium appeared to have been the initial site affected by blood-borne aspergillus. It is of interest that the heart valves or mural endocardium showed no convincing evidence of preëxisting damage in any of these three cases. Only in case 19 were there significant cardiac murmurs and evident peripheral emboli. In this instance the vegetations involved primarily the aortic valve, resulting in aortic insufficiency which led to congestive heart failure and death. In contrast, cases 20 and 21 had endocardial lesions on the right side of the heart; embolization, except to pulmonary vessels in one of them, did not occur.

These three cases were similar in certain respects: all patients had debilitating illnesses, and all had received prolonged antibiotic therapy. Two had leukopenia and received corticotropin for considerable periods of time before the probable onset of endocarditis. Possible portals of entry for fungi were present in all three, either in the form of chronic, open skin lesions, or frequently administered intravenous infusions. No one of these factors can be singled out for incrimination here, though they all may have contributed to an unfavorable alteration in host defense mechanisms.

Cryptococcosis

Recently, the first case of cryptococcal endocarditis (case 22) was reported from the Clinical Center by Lombardo et al.[23] The patient had chronic, symptomatic rheumatic heart disease with moderately severe manifestations of cardiac decompensation. Five months before admission he had developed chills, fever, night sweats, weight loss, headache, and increasing symptoms of congestive heart failure. Significant physical findings were showers of petechiae over the trunk and extremities, cardiomegaly, systolic and diastolic murmurs at the aortic and mitral areas, retinal hemorrhages and exudates, and moderate hepatosplenomegaly. During his three and one-half months in this hospital, 64 blood cultures were taken, as well as 16 urine and six cerebrospinal fluid cultures; all were positive for *Cryptococcus neoformans*. This organism grew readily on the usual media, including

Sabouraud's glucose agar, trypticase soy broth, and blood agar. He was treated with Acti-dione and sulfonamides, without benefit. Throughout his course in the hospital he continued to have myriads of new petechiae as well as multiple retinal hemorrhages, and he developed one classic Osler's node.

At autopsy there was generalized cryptococcosis with cryptococcal endocarditis involving the mitral and aortic valves. Many organisms were found in the vegetations. It was felt that his course was in no way different from that of subacute bacterial endocarditis unmodified by therapy. The total duration of the illness was eight and one-half months.

Histoplasmosis

*Case 32.** A 56 year old white male electrician was admitted to the Clinical Center March 3, 1955, with a diagnosis of Addison's disease secondary to disseminated histoplasmosis. In July, 1952, the patient had developed ulcers on his tongue and buccal mucosa. These were accompanied by fever, weight loss and postprandial vomiting. A diagnosis of ulcerative stomatitis was made and the patient was treated symptomatically for almost a year.

In May, 1953, he was admitted to the University of Virginia Hospital, where a diagnosis of Addison's disease was made. On June 28, 1954, *Histoplasma capsulatum* was cultured from a tissue specimen of an ulceration on the false vocal cords. A urine culture was also positive for the same organism. A histoplasmin skin test gave equivocal results. Treatment with stilbamidine and dihydroxystilbamidine was instituted, but the ulceration of the mouth, pharynx and larynx progressed so that the patient became extremely hoarse and was unable to swallow solids or fluids. One episode of wheezing and cyanosis occurred. There was progressive weight loss and weakness during the next year. He was again admitted to the University of Virginia Hospital, and subsequently transferred to the Clinical Center.

Physical examination revealed an extremely ill man with considerable muscle wasting. He was unable to speak, but indicated that he had severe pain in his throat. The blood pressure was 145/90 mm. Hg; heart rate, 90 per minute; temperature, 37.2° C.; respirations, 20 per minute. A punched-out, scarred lesion was present on the left lateral border of the tongue. The pharynx was edematous and red, and covered by a yellowish exudate. The epiglottis and vocal cords had a similar appearance and showed marked ulceration. The chest was hyperresonant to percussion, and the expiratory phase of respiration was markedly prolonged. The heart was not enlarged. No murmurs, thrills or accentuations of sounds were noted. The liver was enlarged. There was no splenomegaly, lymphadenopathy, petechiae or clubbing of the fingers.

Laboratory examinations revealed a hemoglobin of 14.0 gm. per 100 c.c., and a leukocyte count of 11,200 per cubic millimeter, with 71% polymorphonuclear leukocytes, 24% lymphocytes and 5% monocytes. The erythrocyte sedimentation rate (Westergren method) was 53 mm. per hour; blood urea nitrogen, 25 mg. per 100 c.c.; creatinine, 1.5 mg. per 100 c.c.; uric acid, 6.8 mg. per 100 c.c. Serum electrolyte determinations and the results of liver function tests were normal, with the exception of 11% bromsulfalein retention in the blood at 45 minutes. Urinalysis revealed many leukocytes and occasional erythrocytes, but was otherwise normal. A chest x-ray film showed neither cardiac nor pulmonary abnormalities. An electrocardio-

* Other aspects of this patient's illness have been previously reported by Dr. J. R. York (Virginia M. Monthly **82**: 514–515, 1955), and Dr. K. R. Crispell et al. (case 1, Am. J. Med. **20**: 23–29, 1956).

gram was normal. Cultures of the sputum and urine were positive for *H. capsulatum*. Two blood cultures on Sabouraud's agar were negative after four weeks' incubation. The complement fixation titer using histoplasmin as antigen was 1:16.

During the patient's course in the hospital, replacement therapy for adrenal insufficiency was continued, and feedings were given by a Levine tube. There was one episode of aspiration pneumonia, which cleared rapidly on antimicrobial therapy. However, he developed progressive impairment of renal function, with a rise in the blood urea nitrogen to 152 mg. per 100 c.c., and on the twenty-sixth hospital day he died.

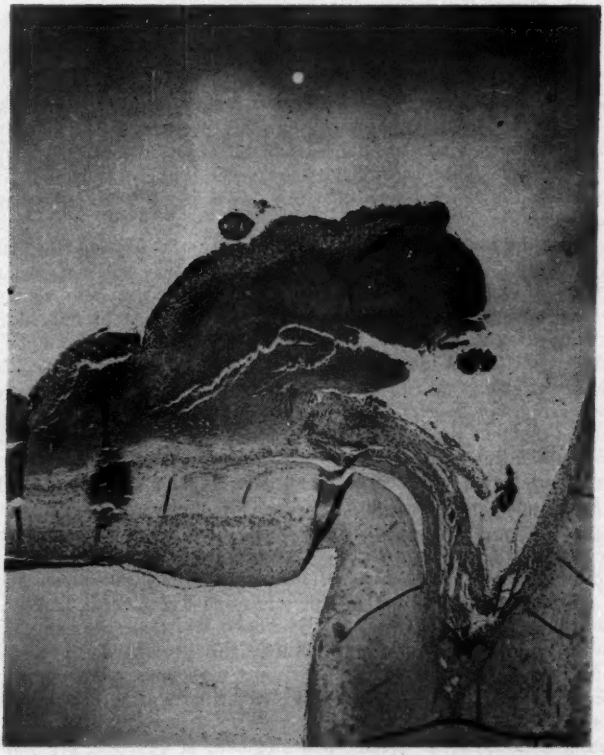

FIG. 3. *Case 32.* Vegetation on aortic valve cusp, × 12, hematoxylin and eosin.

At no time during his hospitalization was cardiomegaly present, nor were murmurs, petechiae or embolic phenomena noted. His heart rate was usually between 85 and 100 per minute, except for occasional tachycardia to 120 beats per minute. Occasional premature auricular contractions were observed.

Postmortem Findings: At autopsy there were lesions of disseminated histoplasmosis. In the heart, both surfaces of the noncoronary cusp of the aortic valve were distorted by a fibrinous vegetative endocarditis (figure 3). Microscopically, this lesion was composed of histiocytes, fibroblasts, fibrin, hemosiderin and lymphocytes. There was collagenous thickening of the valvular endothelium. Yeast cells of *H.*

capsulatum were found in great abundance. There were, in addition, many branching, septate hyphae with round spores on short pedicles characteristic of the mycelial form of *H. capsulatum* * (figure 4).

Histoplasma were also found in the epiglottis, vocal cords, small and large bowel, spleen, liver, prostate gland, testes, adrenal glands, axillary lymph nodes, and in both kidneys, where they had produced necrosis of the renal papillae. There was a bilateral purulent bronchitis and bronchopneumonia in which both *H. capsulatum* and *C. albicans* were present.

Case 33. A 35 year old white railroad engineer was admitted to the Clinical Center on September 2, 1955, with a presumptive diagnosis of staphylococcic endocarditis. In 1944, during military service, he had been hospitalized for investigation

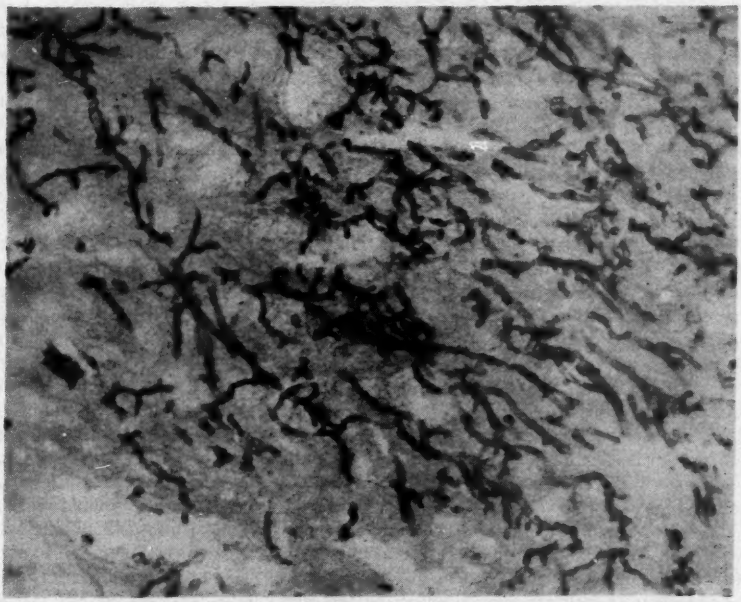

FIG. 4. *Case 32.* Yeast and mycelial forms of *H. capsulatum* in aortic valve vegetation, × 535, Gomori methenamine silver reaction.

of mild hypertension and a heart murmur. Neither was thought to be significant, and he was discharged from the service without apparent disability. The patient had lived in northern Virginia all his life except for service in the South Pacific during World War II, and he had always enjoyed good health.

The present illness had begun in February, 1955, with a four-day bout of fever and malaise, thought to be *la grippe*. A week after onset he felt entirely well and returned to work. Three or four weeks later he had an identical grippelike illness. A day or two before each of these episodes he had spent several hours cleaning a dusty chicken house that had not been used for a year. Symptomatic recovery from the

* These sections have been reviewed by Dr. Chester Emmons, of the National Institute of Allergy and Infectious Diseases, and by Dr. Chapman Binford, of the Armed Forces Institute of Pathology. Both are of the opinion that these are mycelia of *H. capsulatum*, and are not those of *C. albicans*.

second episode was not complete, and from March until May, 1955, he experienced intermittent low grade fever and malaise lasting one or two days and occurring every week or two. There was weight loss of about 10 pounds. Between episodes of fever and malaise he felt relatively well and at times was able to work. Toward the end of May, 1955, he became more severely ill. High fever (103 or 104° F.), lasting for a day or two, began to occur once or twice a week. In June he was hospitalized elsewhere with a tentative diagnosis of subacute bacterial endocarditis based on the presence of fever, heart murmurs and questionable petechiae. Several blood cultures were sterile, and he was discharged after four days without treatment. In July he was hospitalized again, and additional blood cultures were obtained. Eight of these were sterile; from one *Staphylococcus aureus* and *Staphylococcus albus,* presumably contaminants, were isolated. The patient was then treated with penicillin (6,000,000 units daily, intramuscularly) for 21 days, without significant effect on his febrile course. After discharge from the hospital he received a 30-day course of erythromycin and chloramphenicol, again without apparent benefit. Following this, he was admitted to the Clinical Center for further diagnostic studies and treatment.

During the eight-month course of his illness before admission the patient had had no symptoms other than malaise with episodes of fever, and easy fatigability between these episodes. There were no symptoms suggestive of cardiac insufficiency or embolic phenomena. Chilliness accompanied a few bouts of fever, but shaking chills rarely occurred. He complained of occasional frontal headaches, which were readily relieved by aspirin.

Physical examination revealed a somewhat pale, muscular young white male in no distress. The pulse was 100 per minute; temperature, 37.1° C.; respiration, 20 per minute; blood pressure, 150/80 mm. Hg (arms), and 130/80 mm. Hg (legs). No petechial lesions or hemorrhages were seen on examination of the skin, mucous membranes, nail-beds or ocular fundi. Several lymph nodes, measuring 0.5 to 1.0 cm. in diameter, were palpable in the posterior cervical, axillary and inguinal regions. The neck veins were flat, and the lungs were clear to percussion and auscultation. There were no signs of cardiac enlargement, and the rhythm was normal sinus. A harsh grade III systolic murmur was heard best in the aortic area and was transmitted to the neck. A similar systolic murmur was audible maximally at the left sternal border in the third and fourth intercostal spaces, and was heard well in the left paravertebral region. There were no diastolic murmurs, and the heart sounds were not unusual. Liver dullness extended 3 cm. below the right costal margin, and the spleen was palpable 2 cm. below the left costal margin. There was no clubbing of the fingers, edema or cyanosis.

Laboratory Findings: Examination of the urine revealed rare leukocytes, erythrocytes and casts. A mild normocytic, normochromic anemia (hematocrit, 35%) was persistently present. The erythrocyte sedimentation rate was constantly elevated. Total leukocyte counts were within normal limits. Differential leukocyte counts showed eosinophilia as high as 16% (total eosinophils, 772 per cubic millimeter), but were otherwise essentially normal. Serum alkaline phosphatase, thymol turbidity and cephalin flocculation were persistently moderately elevated, while the serum bilirubin and bromsulfalein retention were normal. The serum albumin was 3.0 gm. per 100 c.c.; serum globulin, 4.0 gm. per 100 c.c. The serum creatinine rose from 1.3 mg. per 100 c.c. on admission to 1.8 mg. per 100 c.c. a year later. Blood urea nitrogen also rose during this period from 15 to 24 mg. per 100 c.c. The spinal fluid was not remarkable. Urinary 17-hydroxy steroid excretion following an eight-hour infusion of 40 units of corticotropin was normal on three occasions. The histoplasmin skin test was negative on admission but became positive six months later. A histoplasmin complement fixation test yielded a titer of 1:1,024. Electrocardiograms were essentially normal. Roentgen examination of the chest showed superior mediastinal lymphadenopathy, and angiocardiography revealed minimal coarctation

of the first portion of the descending aorta. There was no evidence of pulmonary parenchymal disease.

Many blood cultures on routine media incubated at 37° C. were negative. In addition, one bone marrow and 18 blood cultures on Sabouraud's glucose agar incubated at 30° C. for from four to six weeks were sterile. No fungi were isolated from mice inoculated intraperitoneally with blood and with bone marrow. Two cervical lymph nodes were excised, and on microscopic examination these showed multiple noncaseous granulomas. Although a careful search of many sections stained for fungi revealed no organisms, *H. capsulatum* was isolated on Sabouraud's glucose agar from one of these nodes. This organism was also isolated from urine inoculated into mice. No fungi were isolated from sputum, throat swabs or spinal fluid.

Course: From his first admission on September 2, 1955, until his death on October 24, 1956, the patient was hospitalized six times for a total of 284 days. During the first three months of observation there was true intermittent fever, with abrupt temperature elevations as high as 40.5° C. This fever occurred every one to three weeks and disappeared after 24 to 48 hours.

From December, 1955, to April, 1956, with the patient at bed-rest, there was a period of clinical improvement, manifested by considerable lessening in the frequency and degree of fever, reduction in splenomegaly, and gain in weight. Heart murmurs remained unchanged. On rare occasions, a few minute (1 mm.) petechiae without white centers appeared on the arms and legs and faded completely in three days. Also rarely, minute linear brownish lines were seen beneath the distal portion of the finger-nails. The patient was usually able to relate their appearance to trauma. Laboratory studies, however, did not reflect the improvement that was evident clinically. Abnormalities in the results of renal and hepatic function tests, elevated sedimentation rate, and mild anemia remained relatively constant.

In May, 1956, clinical deterioration began with the appearance of a sore throat and higher and more frequent fever. The serum creatinine rose gradually from 1.4 to 1.8 mg. per 100 c.c. On May 4, laryngoscopy revealed an ulcerative lesion of the epiglottis which on biopsy showed granulomatous inflammation, and organisms resembling *H. capsulatum* were seen in macrophages. Culture of the specimen was positive for *H. capsulatum.* Paroxysmal atrial fibrillation also began at this time. Such episodes were prevented subsequently by the administration of digitoxin. Because of his unfavorable clinical course, and because of the availability of Amphotericin B, which appeared promising in the treatment of certain fungal infections,[43, 46] this antibiotic was administered to the patient orally from May 29 until his death on October 24, 1956. He received 2.4 gm. of Amphotericin B daily for 101 days, then 5.0 gm. daily for 48 days.

During this period of therapy with Amphotericin B the patient gained 5.6 Kg. in weight and was entirely free of fever. Laryngoscopy on June 14 showed complete healing of the epiglottal lesion. The erythrocyte sedimentation rate (Westergren method) fell from its peak of 65 mm. per hour in May to 28 mm. per hour shortly before death. Other laboratory studies were unchanged; mild anemia and evidence of impaired renal and hepatic function remained. With the possible exception of minimal changes in the intensity of the heart murmurs, the physical findings also remained unchanged. On October 24, 1956, the patient felt well, as he had for months. Suddenly that evening he called for a nurse and collapsed. The pulse and blood pressure were unobtainable. Despite attempts at resuscitation, he died a few minutes later.

Comment: This patient presented an extremely difficult diagnostic problem. Before completion of definitive studies, Hodgkin's paragranuloma and sarcoidosis were entertained as diagnostic possibilities. Once the diagnosis

of histoplasmosis had been established, and the possibility of subacute bacterial endocarditis was reasonably well excluded by negative blood cultures, mycotic endocarditis of the aortic valve due to *H. capsulatum* was seriously considered. However, as noted above, attempts to culture this organism from the blood were unsuccessful, and it was felt that the patient might have a congenital deformity of the aortic valve in association with coarctation of the aorta. Thus, opinion was divided as to whether there was histoplasma endocarditis of the aortic valve (with or without congenital deformity), or just congenital deformity causing the aortic murmur. In

FIG. 5. *Case 33.* Vegetation on aortic valve.

addition, it was felt that fever and splenomegaly could be attributed to generalized histoplasmosis and therefore were not necessarily evidence of endocarditis. The immediate cause of death was thought to be a ventricular arrhythmia.

Postmortem Findings: At autopsy, the principal lesion was a large, irregular, partially calcified, friable vegetation on the aortic valve (figure 5), which measured 3 cm. by 2 cm. in diameter and involved all three cusps, two of the three commissures, and the sinus of Valsalva adjacent to the left coronary ostium.

Microscopically, the vegetation was composed of large areas of eosinophilic and basophilic granular debris, interspersed with collections of macrophages, multinucleated giant cells and polymorphonuclear leukocytes. At the base of the vegetation, vascular connective tissue with foci of granulomatous inflammation was present,

with evidence of marginal organization of the necrotic portions of the vegetation. In the hematoxylin- and eosin-stained sections, collections of *H. capsulatum* were seen in some of the macrophages and multinucleated giant cells. *H. capsulatum* yeast cells were better demonstrated in sections prepared by the Gomori methenamine silver method (figure 6). In the necrotic portions of the vegetation, scattered extracellular organisms morphologically resembling *H. capsulatum* were seen in the methenamine silver preparation, but could not be identified in the hematoxylin-eosin sections.

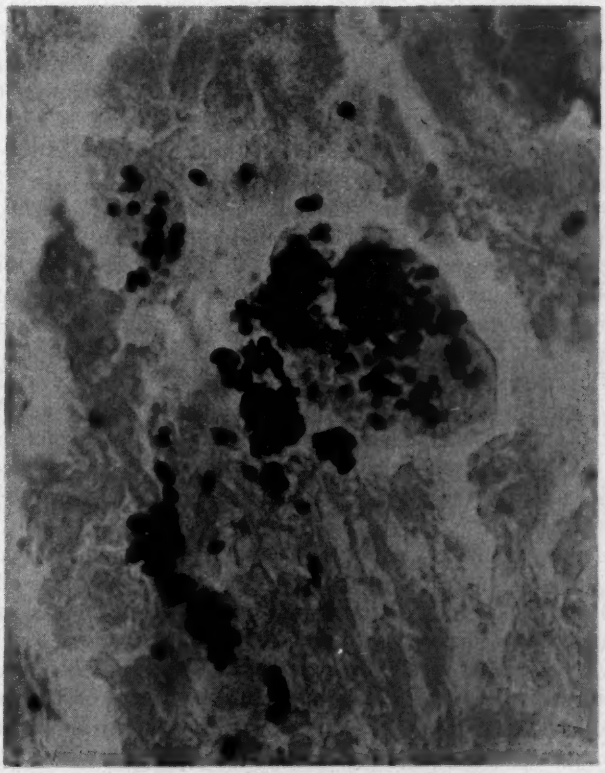

FIG. 6. *Case 33.* Yeast forms of *H. capsulatum* in aortic valve vegetation, × 725, Gomori methenamine silver reaction.

Numerous foci of granulomatous inflammation were scattered throughout the myocardium, usually associated with necrosis of myocardial fibers. No organisms could be found in these myocardial granulomas, and no mycotic emboli were seen in the myocardial vessels.

Focal granulomatous inflammation with multinucleated giant cells and epithelioid cells was found in the liver, spleen, kidneys, pancreas, thyroid gland, lungs and mediastinal lymph nodes. No organisms could be found in these lesions.

Specimens of liver, spleen, adrenal gland, hilar lymph node, epiglottis, brain and aortic valve vegetation were cultured on several media for fungi and were inoculated

intraperitoneally into mice. *H. capsulatum* was cultured from the vegetation and from the liver. This fungus was also isolated from mice inoculated with specimens of the vegetation and adrenal gland. No fungi were isolated from the other specimens.

Discussion

In 10 of the 11 reported cases of endocardial histoplasmosis, adequate clinical and pathologic data are available for evaluation. In three of these (cases 25, 29 and 32) the cardiac histoplasmosis was a secondary finding in patients who had extensive pathology in other organs. In two of the three the diagnosis of generalized histoplasmosis was made ante mortem, and in none was there any reason by history or physical examination to suspect cardiac involvement, or any indication that the cardiac lesions found at necropsy played a major role in the patient's course. None of the three had preëxisting valvular disease.

In the other seven patients (cases 23, 24, 26, 27, 28, 30 and 33) the cardiac involvement appeared to be of major significance in the patients' course. Six of the seven (cases 23, 26, 27, 28, 30, 33) had some of the classic manifestations of endocarditis, such as changing murmurs, spiking fever, emboli, hematuria, clubbing of the fingers, anemia, splenomegaly, etc. In four there was preëxisting valvular damage: in three due to rheumatic fever, and in one to luetic aortitis and valvulitis. Since these six had manifestations compatible with endocarditis, the question arises as to why the diagnosis was not made ante mortem in any of them. In two of the patients (cases 26 and 30) it appears that this diagnosis was not seriously considered. It would seem that in these cases the significance of the physical findings was not fully appreciated.

Of the four patients (cases 23, 27, 28 and 33) in whom endocarditis was suspected, the diagnosis of generalized histoplasmosis was made in two (cases 23 and 33). In all four numerous blood cultures were taken, but only in case 33 were these taken specifically for fungi. In all four the blood cultures were negative. It would appear that patients who have negative routine blood cultures and a clinical picture compatible with endocarditis should be investigated thoroughly by culture and biopsy for mycotic infection. It should be emphasized that even blood cultures on fungal media may not provide an etiologic diagnosis, and these should be supplemented by fungal cultures of the throat, sputum, urine, etc. In addition, lymph nodes, skin lesions, etc., should be cultured and stained specifically to demonstrate fungi. Serologic tests for fungi should also be utilized. When endocarditis is suspected but blood cultures are negative, the organisms may be demonstrated elsewhere by these supplementary studies. This occurred in our patient (case 33) in whom blood cultures were negative, but cultures of lymph node and urine were positive for *H. capsulatum,* and complement fixation tests were strongly indicative of active histoplasmosis.

In this patient (case 33) the absence of positive blood cultures precluded

an unequivocal diagnosis of histoplasma endocarditis. It is well known that fungi are frequently extremely difficult to culture from body fluids or tissues, especially blood. Improvement in these technics is at present under investigation at the National Institute of Allergy and Infectious Diseases, and will be discussed in a subsequent publication.[47] However, the demonstration of the disease elsewhere, and the clinical picture compatible with endocarditis, would favor a presumptive diagnosis of histoplasma endocarditis. This, in turn, would be an indication for vigorous therapy. At the time of the patient's hospitalization, Amphotericin B was under investigation. It has subsequently been shown that this antibiotic, which is very effective in animal histoplasmosis,[43, 46] is absorbed poorly when given by mouth. In severe disease such as endocarditis, intravenous rather than oral Amphotericin B is the best experimental therapy now available.[48]

In summary, histoplasma involvement of the endocardium may occur with or without previous valvular damage. It may be a minor manifestation of overwhelming disease, or it may be of major clinical significance.

Mucormycosis

A single case of mucormycosis involving the endocardium appears in the literature.[32] The patient, a 64 year old man with advanced multiple myeloma, had received antibiotic and corticosteroid therapy. At necropsy, hyphae typical of mucor were seen microscopically in focal endocardial lesions of the left atrium and ventricle. Although thrombi containing the fungus were present in the coronary, pulmonary, splenic, gastric and meningeal vessels, the author felt that the mycotic infection did not contribute significantly to the patient's death.

Summary and Conclusions

Thirty-one previously reported cases of fungal endocarditis are reviewed and three additional cases (two due to *H. capsulatum* and one to *C. immitis*) are reported. The fungi implicated are candida, blastomyces, coccidioides, aspergillus, cryptococcus, histoplasma and mucor. Candida and histoplasma endocarditis are the most common, each comprising about a third of the 34 cases. In some cases endocarditis is not clinically evident, and occurs as an apparently minor manifestation of overwhelming generalized mycotic infection. However, the majority of the cases resemble subacute bacterial endocarditis, and in these cases endocarditis was an important manifestation of their mycotic disease.

Aside from cases where the diagnosis of fungal endocarditis is readily apparent, there are two clinical situations in which it should be seriously considered. One such is seen in the patient with known systemic fungal disease who has physical signs suggestive of endocarditis. Significant heart murmurs and evidence of major emboli are the most important physical

findings, because several other findings usually associated with endocarditis (fever, anemia, splenomegaly, etc.) also occur commonly in systemic fungal disease without endocarditis.

The other clinical situation that should suggest the diagnosis of fungal endocarditis is seen in the patient with a clinical picture of subacute bacterial endocarditis whose routine blood cultures are sterile and who has no obvious evidence of mycotic infection. In such a case blood cultures for fungi should be obtained, and a careful search should be made for evidence of fungal infection elsewhere by culture of urine, bone marrow, lymph nodes, etc., and adequate histologic examination of tissue obtained by biopsy. If evidence of systemic mycotic infection is found, it may be an important clue to the nature of the endocardial process.

Establishing the diagnosis of mycotic infection is becoming increasingly important as specific therapy becomes available. It is felt that awareness of endocarditis as a manifestation of fungal disease, and the use of cultural and histologic technics appropriate for the demonstration of fungi, will allow the diagnosis of fungal endocarditis to be made more frequently during life.

Acknowledgments

The authors wish to express their gratitude to Dr. C. H. Binford, of the Armed Forces Institute of Pathology, who kindly made available to us the clinical information on cases 28, 29 and 30 (tables 1A and 1B).

Amphotericin B was supplied by the Squibb Pharmaceutical Co., New Brunswick, New Jersey. Acti-dione was obtained from the Upjohn Co., Kalamazoo, Michigan.

Summario in Interlingua

Es presentate un revista de 31 previemente reportate casos de endocarditis fungal. Tres casos additional (duo causate per *Histoplasma capsulatum* e un per *Coccidioides immitis*) es reportate. Le fungos representate esseva candida, blastomyces, coccidioides, aspergillus, cryptococcus, histoplasma, e mucor. Endocarditis a candida e a histoplasma esseva le plus frequente. Cata un de iste gruppos contava circo un tertio del total de 34 casos. In certe casos, endocarditis non esseva clinicamente evidente e occurreva como un apparentemente minor manifestation de un invasion general de infection mycotic. Tamen, le majoritate del casos resimilava subacute endocarditis bacterial, e in istos, endocarditis esseva un manifestation importante del morbo mycotic. Esseva incontrate duo situationes clinic in que endocarditis fungal deberea esser considerate como un serie possibilitate. Le un se trova in patientes con cognoscite morbo fungal systemic qui exhibi signos physic que justifica le suspicion de endocarditis. Significative grados de murmure cardiac e evidentia de major embolos es le plus importante tal constatationes physic. Le secunde se trova in patientes exhibiente le tableau clinic de subacute endocarditis bacterial, sterile culturas routinari de sanguine, e nulle obvie manifestationes de infection mycotic. In tal casos culturas sanguinee pro fungos debe esser effectuate, e un meticulose scrutinio debe esser instituite pro signos de infection fungal in altere partes del organismo. Isto require culturas de urina, de medulla ossee, de nodos lymphatic, etc. e un adequate examine histologic de specimens de histos obtenite per biopsia. Establir le diagnose de infection mycotic deveni de plus in plus importante, viste que therapias specific es facite disponibile. Es exprimite le opinion que le consideration de endocarditis como manifestation possibile de morbo fungal e le uso de technicas cultural e histologic va permitter le plus frequente effectuation del diagnose de endocarditis fungal durante le vita del patiente.

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ATRIAL SEPTAL DEFECT IN THE AGED *†

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AN atrial septal defect is now recognized as one of the most common forms of congenital heart disease. This lesion may permit the patient to live to old age without producing any appreciable handicap. It also appears that an atrial septal defect is the type of congenital heart disease most frequently found in middle age. In a large municipal hospital over a four-year period, we have recognized 19 patients over the age of 45 years with this disorder. Eleven of the patients were male and eight were female. Two of the diagnoses were made by postmortem examination and 12 by cardiac catheterization; the remaining five satisfied the clinical criteria for this diagnosis. (During the same period we recognized among patients in the same age range one example of each of the following congenital abnormalities: tetralogy of Fallot, Eisenmenger's syndrome, and idiopathic dilatation of the pulmonary artery.) This experience does not appear to be unique, since there are numerous comments in the literature on the longevity of subjects with this disorder.[1] Table 1 is compiled from Wood's data.[2] It

TABLE 1

Age Incidence of Patients with Congenital Heart Disease*

	% of Series 50 Years or over	Number of Patients in Series
Atrial septal defect	8.5	167
Ventricular septal defect	1.0	72
Patent ductus arteriosus	1.0	115
Pulmonic stenosis	1.0	144
Tetralogy of Fallot	0.0	99

* Table compiled from *Diseases of the Heart and Circulation*, 2nd Ed., by P. Wood.

is offered as further evidence that, of the common types of congenital heart disease, atrial septal defects offer the best prognosis for a long life. The oldest patient in our series was 72 when first seen by us; he is now 76, and appears to be in fair health, having survived two surgical procedures uneventfully (cholecystectomy and herniorrhaphy). The oldest patient reported with this disorder was 82 years of age.[3]

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Clinical Features

In eight of the 19 subjects in this series, hospitalization was for reasons not related to the cardiac disorder. These patients experienced little or no discomfort from their heart disease. Most patients admitted to shortness of breath on exertion, but were able to maintain the same pace as their contemporaries. Five were hospitalized for bronchopneumonia, which occurs frequently in this disease, probably because of the pulmonary plethora. One woman sought medical attention because of severe exertional dyspnea and weakness. These symptoms were attributed to her heart disease until it was learned that she had marked anemia, secondary to menorrhagia. After removal of a myomatous uterus and restoration of her blood volume, she returned home to her family of eight children, symptom-free. Another patient was referred to the hospital with the diagnosis of mediastinal tumor. The tumor masses turned out to be massive pulmonary arteries. Only four of this series sought attention because of symptoms directly attributable to heart disease.

Only one patient exhibited the gracile type of body habitus frequently encountered in atrial septal defect in children; and in this patient it resulted from a severe myositis with marked muscular atrophy, rather than from skeletal underdevelopment.

Clubbing and cyanosis of the extremities were present in four patients, all of whom were severely symptomatic. Two of these died while under observation. Therefore, the presence of these signs should indicate a grave prognosis. An elevated jugular pressure and peripheral edema were observed in three of these four, and in no others of this series.

In seven of the 19 patients, signs of chronic bronchitis and emphysema were noted. These included changes in the shape of the thorax, with low, relatively immobile diaphragms, high-pitched breath sounds with prolongation of the expiratory phase, and thick basilar râles. Although none of this group was evaluated with complete pulmonary function studies, it is our impression that pulmonary dysfunction is frequently responsible for the dyspnea of these patients.

Palpation of the precordium is a rewarding maneuver. This usually demonstrates a systolic heave over the dilated and hyperdynamic right ventricle. A systolic lift is frequently perceived over the pulmonary artery. With pulmonary hypertension and gross dilatation of the pulmonary artery, the shock of the second sound may be felt in the same area. Movement of the left ventricle is not palpable, and if a left ventricular heave is present, one should be alert for other lesions, or for the ostium primum type of an atrial septal defect.

The two most important auscultatory signs of an atrial septal defect are a pulmonary systolic murmur and a widely split second sound.[4, 5] A murmur was heard in all cases of this series. It was usually a Grade II or III in intensity, and was never accompanied by a thrill. In fact, the presence

of a pulmonic thrill should arouse suspicion of an associated pulmonic stenosis. Wide splitting of the second sound was noted in 14 cases.

The first heart sound is usually normal or loud in intensity. It is frequently split, and the second component of the split first sound may be most

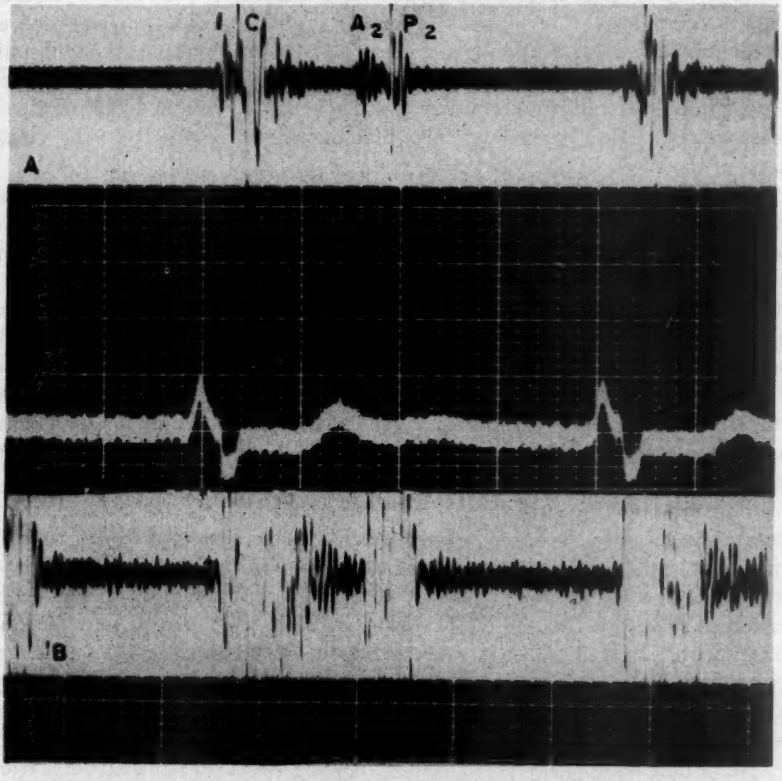

FIG. 1. Phonocardiogram of a 74 year old male with an atrial septal defect. A large pulmonary flow is present, but no pulmonary hypertension. Both A and B were recorded over the pulmonic area. The sensitivity of the galvanometer was reduced in A to illustrate better the various components of the trace. I refers to A-V valvular closure, C to pulmonary artery ejection sound, A_2 and P_2 to aortic and pulmonic semilunar closure sounds.

Note that the pulmonic ejection sound, or "click" is much more intense than is I, and also the closeness of the click to the A-V closure sound. Also note the wide splitting of the second sound. The greater intensity of P_2 than A_2, and the presence of a loud first sound (both I and C together) over the pulmonic area are auscultatory signs of a dilated pulmonary artery.

intense in the pulmonic area. This latter sound probably represents an exaggerated vascular element of the first sound. The first heart sound is usually dominated by auricular ventricular valve closure, but phonocardiographic traces do demonstrate low intensity vibrations (vascular element of first sound) associated with the rise in pressure in both the aorta and the

pulmonary artery. When either of these vessels is markedly dilated and lies close to the chest wall, this component may be quite loud. Because of the proximity of the pulmonary artery to the chest wall, vibrations from this structure are more easily heard than are those from the aorta. A loud first sound at the base of the heart is a sign of dilatation of one of these vessels. This is demonstrated in figure 1, which is a phonocardiogram recorded at the pulmonic area of a man with a high pulmonary blood flow but no pulmonary hypertension. The sound marked "C" occurred immediately after the beginning of pulmonary artery systolic pressure rise and before aortic pressure rise. It is likely, therefore, that this sound results from the vibrations of the dilated pulmonary artery.

When the pulmonary artery pressure is elevated and the period of isometric contraction of the right ventricle is prolonged, then this sound is widely separated from the first heart sound (A-V valve closure) and is heard distinctly as a click.[6] Such a click is shown in figure 2, which is a trace obtained from a patient with an atrial septal defect, severe pulmonary hypertension and a normal pulmonary blood flow. It shows the first sound occurring at 0.07 second after the beginning of the QRS, but the click at 0.15 second. Data obtained by cardiac catheterization demonstrated right ventricular contraction beginning at 0.07 to 0.08 second, and the pulmonary artery pulse at 0.14 second after the upstroke of the R wave of the electrocardiogram.

The systolic murmur can be seen to originate with this sound and to end before the second sound. This represents an "ejection type" of murmur—that is, it begins with the commencement of blood flow into one of the major vessels, is at its greatest intensity in midsystole, and fades before the second sound. When the volume of the shunt is great, the murmur may be quite prominent. It is usually credited to the turbulence resulting from a high pulmonary flow. However, dilatation of the pulmonary artery also plays a role in its genesis, for the murmur is usually present in patients with pulmonary hypertension and normal pulmonary blood flow. Vigorous exercise in normal subjects may raise the blood flow to levels equal to that encountered in cases of atrial septal defect without producing a significant murmur. Subjects with chronic hemolytic anemia (e.g., sickle cell or Cooley's anemia) frequently exhibit pulmonic systolic murmurs and dilatation of the pulmonary artery. If the hemoglobin is raised to normal levels by transfusion, the murmur remains, although less intense. This would seem to be evidence that two features play a part in the production of the murmur, namely, high flow and structural alteration of the vessels.

The second sound is usually widely split in cases of atrial septal defect. By wide splitting, we mean intervals 0.05 second or greater between the aortic and pulmonic components of the second sound. This occurred in 14 of the 19 cases. The pulmonic component of the second sound is not loud, unless pulmonary dilatation and/or pulmonary hypertension is present.

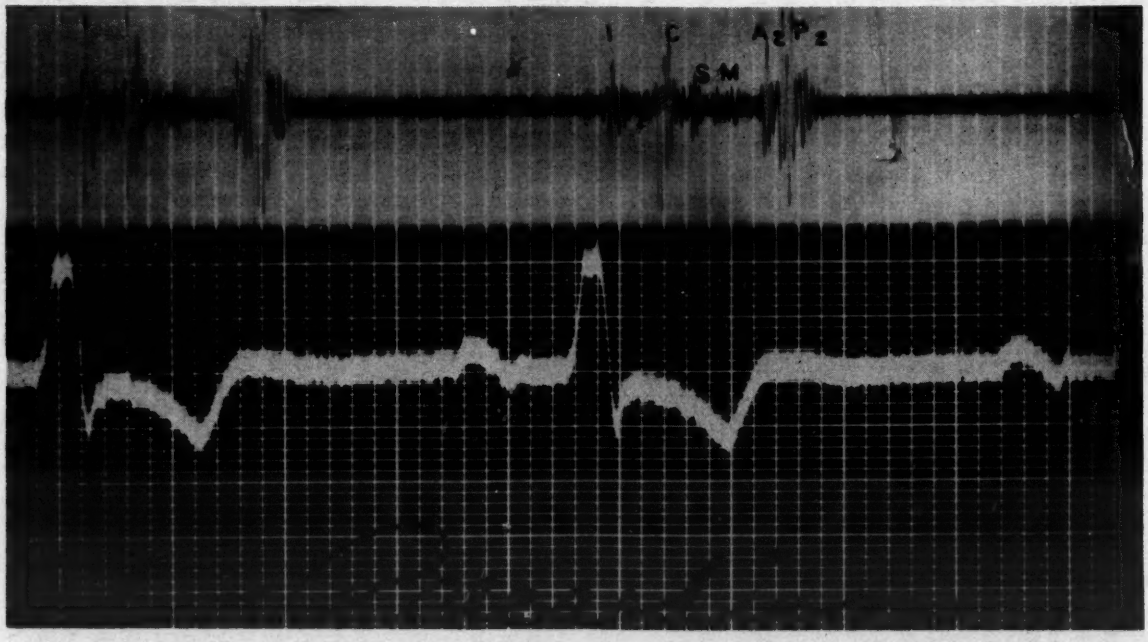

FIG. 2. Phonocardiogram recorded over the pulmonic area of a patient with an atrial septal defect. Severe pulmonary hypertension and right heart failure were present. I refers to A-V valvular closure, C to pulmonic click, S M to systolic murmur, A_2 and P_2 to aortic and pulmonic semilunar closure sounds. The loud click and P_2 with minimal splitting of the second sounds are auscultatory evidence of the complication of pulmonary hypertension in atrial septal defect. A short, high-pitched diastolic murmur follows P_2, but this is not well demonstrated on this trace.

Further discussion in the text.

Figure 1 shows the loud P_2 occurring 0.06 second after A_2. This patient had marked enlargement of the pulmonary artery but no pulmonary hypertension. When pulmonary vascular resistance increases and the pulmonary flow decreases, the splitting diminishes. This is demonstrated in figure 2.

The splitting of the second sound has been explained in part by the right bundle branch block which is almost always found in this disorder, and also by the greater volume of blood ejected from the right ventricle. The more important factor, in our opinion, is the greater volume of blood handled by the right ventricle, thus prolonging its ejection period. The evidence for this opinion can be summarized briefly:

1. In patients with atrial septal defect with pulmonary hypertension, the splitting is less prominent than in those subjects with high pulmonary blood flows, regardless of the electrocardiographic picture.

2. In atrial fibrillation the interval between A_2 and P_2 varies directly with the length of the preceding diastole. This phenomenon occurs in subjects without significant pulmonary hypertension.

3. The splitting of the second sound diminishes following surgical correction of the defect, with little change in the electrocardiogram.

4. Cardiac catheterization of these individuals often demonstrates no delay in the onset of right ventricular contraction.

A short diastolic rumble may be heard along the left sternal border. Because of this, mitral stenosis has been frequently misdiagnosed in the past. This low-pitched sound usually becomes more intense on inspiration, unlike the murmur of mitral stenosis, which is diminished by this maneuver. This phenomenon is most likely a gallop due to rapid right ventricular filling. The associated features found with gallop activity—such as a palpable thrust of the heart against the chest wall at the time of the sound, and large diastolic waves of the ballistocardiogram—are present.

With gross dilatation of the pulmonary artery and pulmonary hypertension, a high-pitched murmur beginning with the second sound is likely to be heard. Such a murmur was heard in eight of our patients. The murmur is due to pulmonary valvular incompetence.

The electrocardiogram is a great diagnostic aid in this disorder. It has received much attention in the recent literature.[7, 8] The usual picture is that of a right bundle branch block pattern, either complete or incomplete. If absent, the diagnosis should be held in question. Fourteen of our patients showed a complete right bundle branch block, and five showed incomplete right bundle branch block. Right ventricular hypertrophy was diagnosed in eight cases of the series. With normal sinus rhythm the P wave is unremarkable unless pulmonary hypertension is present, when it becomes tall and peaked. Atrial fibrillation occurs frequently in this age group, although it is rare in young patients with this disorder.[2] Fourteen of our patients exhibited this arrhythmia.

Radiography and fluoroscopy are extremely helpful in arriving at the

diagnosis of an atrial septal defect. For many years major diagnostic emphasis was placed on these technics, with relatively little attention paid to other diagnostic aspects of this disorder.[9, 10] Characteristically, the x-ray picture is that of cardiomegaly. The right atrium and right ventricle are

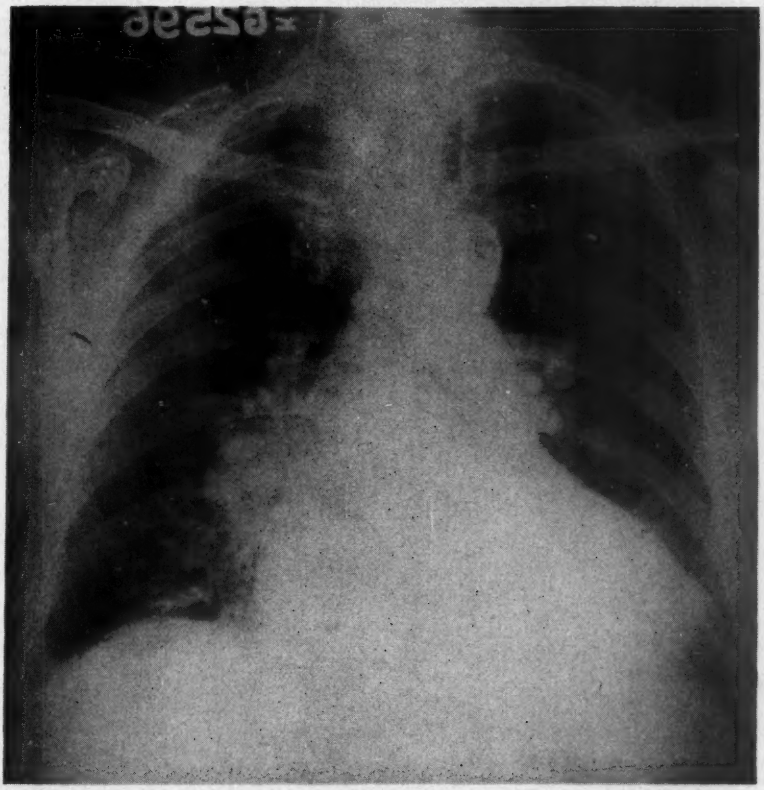

FIG. 3. Chest film of a 74 year old male with an atrial septal defect. The pulmonary flow was 7.0 L./Min./M^2. The pulmonary artery pressure was 45/19. The pulmonary vascular resistance was calculated to 103 dynes/sec./cm.^{5}/M^2. Arterial O_2 saturation was 98%. Moderate arterial hypertension is present, which probably accounts for the normal size of the aorta.

Note the huge pulmonary arteries, with visualization of the fine branches extending to the peripheral lung fields.

markedly enlarged, whereas the left atrium and left ventricle are small or normal. The aorta is usually hypoplastic in the young, but often of normal configuration in the aged.

The high pulmonary blood flow is reflected in an enlarged pulmonary vascular tree. The main pulmonary artery and the secondary and tertiary branches are dilated and tortuous. Pulsation of these structures is often

found on fluoroscopy. If pulmonary hypertension is present, only the tertiary branches are reduced in caliber—not the secondary branches. Only the very periphery of the lung appears clear. The secondary branches of the pulmonary arteries will still be found pulsatile in the presence of severe

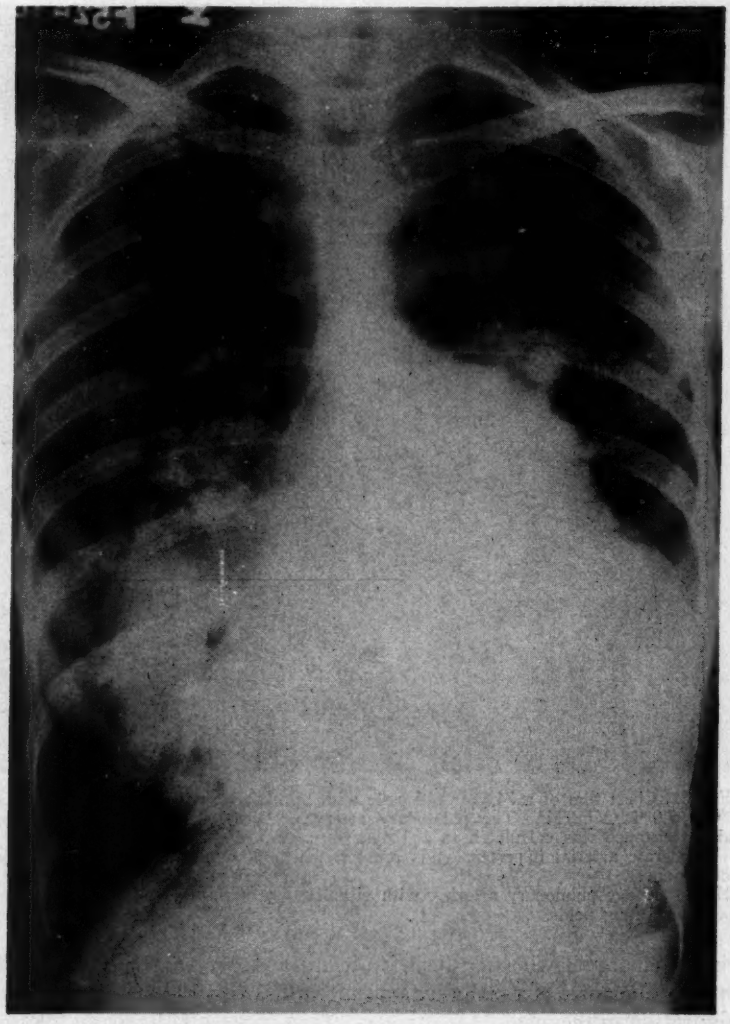

FIG. 4. Roentgenogram of 52 year old woman with atrial septal defect. The pulmonary blood flow, 10.6 L./M/M^2; pulmonary artery pressure, 88/46; calculated pulmonary resistance, 160 dynes/sec./cm.^{5}/M^2. Arterial oxygen saturation was 92%.

Note the aneurysmal dilatation of the pulmonary arteries. The pulmonary radicles are seen to extend to the periphery of the lung fields.

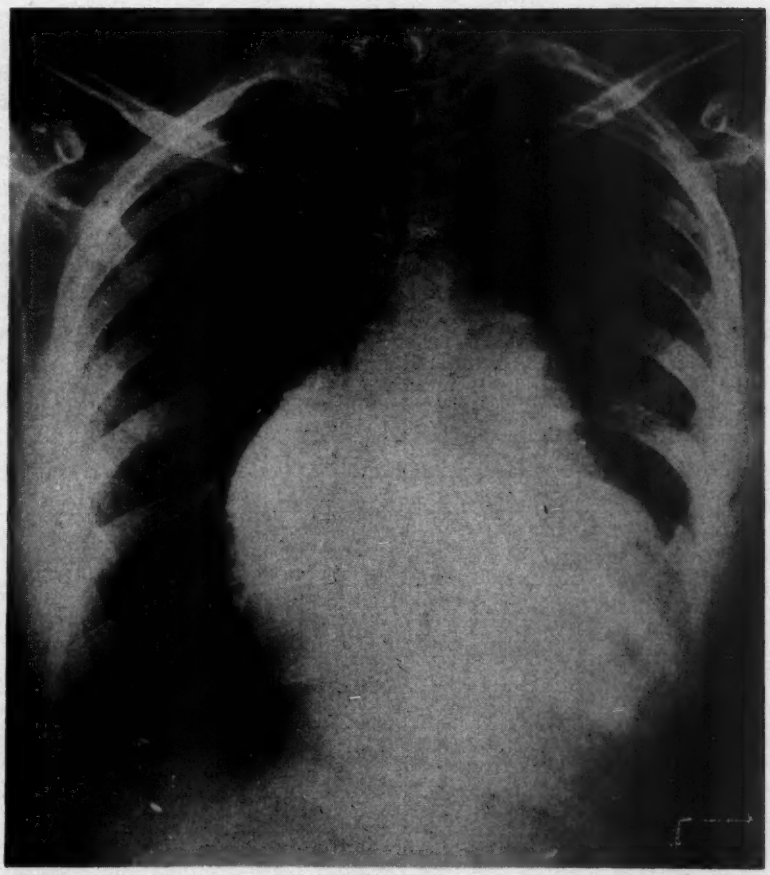

FIG. 5. Chest film of a 19 year old girl with primary pulmonary hypertension proved at autopsy. The pulmonary blood flow was determined to be 2.8 L./M/M^2; pulmonary artery pressure, 127/81; pulmonary resistance, 2316 dynes/sec./cm.^{5}/M^2. This film is similar to figures 3 and 4 in that massive enlargement of the pulmonary arteries is present.

Note the ischemia of the peripheral lung fields. Unlike the films of the subjects with atrial septal defect, the tertiary branches of the pulmonary arteries are not visible.

pulmonary hypertension. Caution is needed then in interpreting this clinical sign as one of an increased blood flow.

This striking increase in the size of the pulmonary vascular tree can be only partially explained by the increased blood flow. In children with large intracardiac shunts and huge pulmonary flows, the pulmonary vascular tree is not so prominent. Thus, the increase in size noted in the aged is probably due to aging of these structures. The elastic tissue of the pulmonary arteries is replaced with fibrous tissue, such as is commonly found in the aortas of

aged hypertensive subjects. Figures 3, 4 and 5 illustrate many of the aforegoing points.

Venous angiocardiography has been employed by us in a number of these patients, but it was rarely helpful except in cases of significant right-to-left shunts, where early opacification of the left atrium occurs. This technic may occasionally demonstrate anomalous pulmonary venous drainage, so that it is a worthwhile test for patients being considered for surgery. More

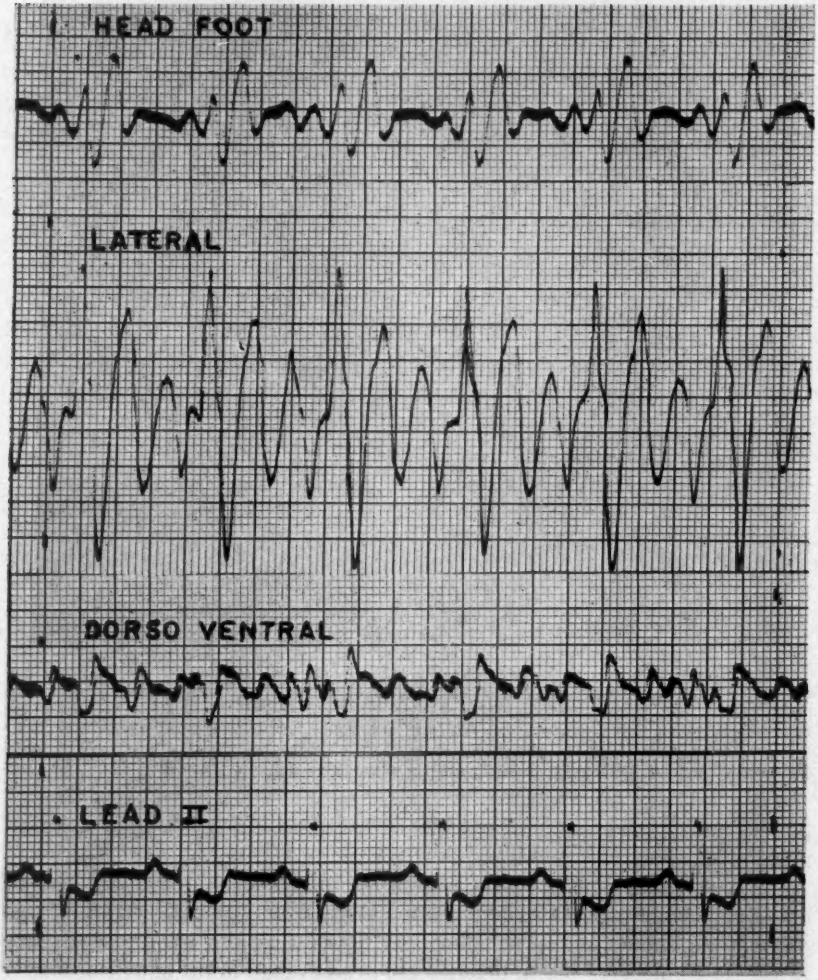

FIG. 6. Three-plane ballistocardiogram of an elderly male with an atrial septal defect. Upward indicates headward, rightward and backward motion of the body.
Note the huge systolic complexes in the lateral trace.

useful than venous angiocardiography is selective angiocardiography, with the opaque material discharged directly into the pulmonary artery through a cardiac catheter. With this technic the right atrium is opacified immediately after visualization of the left atrium.

Ballistocardiograms have been recorded from the majority of the patients in this series. At first, motion in the head-foot plane was recorded with a Dock type of ballistocardiograph. Later, we recorded the motion of the body in three planes (head-foot, lateral and dorsoventral) with an instrument of Dr. William Dock's invention.[11] Such traces are extremely helpful but not diagnostic. It is likely that we would have missed the proper diagnosis in a few cases had it not been for the three-plane ballistocardiogram. The usual picture is that of large amplitude systolic complexes in all planes, but especially in the lateral trace. Such a pattern should suggest that large amounts of blood are being moved about in the thorax. Figure 6 illustrates a typical record obtained from an elderly subject with moderate pulmonary hypertension but with twice the expected pulmonary blood flow.

The diagnosis of an uncomplicated atrial septal defect can be confirmed by cardiac catheterization if blood samples from the right atrium have a greater oxygen content than do samples from the inferior and superior vena cavae. This means oxygenated blood is entering the right atrium through an atrial septal defect, or occasionally from the anomalous insertion of a pulmonary vein or veins into the right atrium. This latter condition can often be determined either by the characteristic x-ray picture, or by introduction of the cardiac catheter directly into the anomalous vein from the right atrium.

The diagnosis of Lutembacher's syndrome is frequently suggested in patients with large left-to-right shunts through an atrial septal defect. These cases usually have massive enlargement of the right heart and pulmonary arteries, and a diastolic gallop which is confused with the rumble of mitral stenosis. The diagnosis of Lutembacher's syndrome can be proved or rejected by passing the cardiac catheter into the right atrium through the defect and into the left atrium and left ventricle. If mitral stenosis is present, then the end diastolic pressure of the left atrium will be greater than the end diastolic pressure of the left ventricle. In only eight of the 12 patients who were catheterized were we able to obtain such data. No cases of Lutembacher's syndrome were found. The high incidence reported in the early literature probably resulted from misinterpreting the fibrous and calcific beading of the mitral leaflets as mitral stenosis.[10, 12] Such changes are common in elderly subjects.

In only nine of the 12 subjects were the data complete enough to estimate the volumes of shunt, pulmonary flow and pulmonary resistance. These data are shown in table 2 and are arranged in order of the age of the patients. The two patients over 70 years of age both had high pulmonary blood flows, with normal pulmonary vascular resistance and normal arterial oxygen

saturation. Examples such as this clearly demonstrate that large pulmonary blood flows over a long period of time do not necessarily result in pulmonary hypertension.

In the patients with arterial oxygen desaturation, the highest values for pulmonary resistance were calculated. This supports the suggestion of Dexter [13] that marked arterial desaturation in atrial septal defect is best explained by a right-to-left atrial shunt resulting from right ventricular failure.

Two patients with large shunts had elevated left ventricular and diastolic pressures (above 10 mm. Hg). An elevated ventricular end diastolic pressure in the absence of constrictive pericarditis or pericardial tamponade is usually interpreted as an indication of ventricular failure. It would seem reasonable that the left ventricular failure increased the volume of the shunts in these instances. This thesis was advanced in 1956 by Dexter,[18] and our observation supports it.

TABLE 2

Case	Age	Pulmonary Artery Pressure mm. Hg			Pulmonary Flow L./M/M²	Pulmonary Resistance dynes/sec./cm.⁵/sq. meter	Arterial O_2 Saturation
		Systolic	Diastolic	Mean			
Normal values	—	18–30	6–12	12–18	3.1±0.4	below 100	94–100%
1	74	45	19	26	7.0	103	98
2	72	62	27	41	10.1	89	94
3	65	95	40	55	4.3	326	86
4	63	75	40	52	3.4	531	86
5	58	92	47	66	2.9	740	74
6	53	47	17	22	4.4	120	93
7	52	88	46	65	10.6	160	92
8	51	39	12	21	12.0	51	94
9	47	75	40	53	5.0	228	96

In a few instances, blood aspirated from pulmonary veins was slightly unsaturated. This may mean that the pulmonary transit was so rapid that the blood did not become fully oxygenated. It is also possible that the incomplete oxygenation of the pulmonary venous blood resulted from passage through diseased lung.

A long, active life is led by many patients with atrial septal defects. The average age at death, usually given as 36 years,[9, 12] is longer than that found in the other major types of congenital heart disease. Associated anomalies probably play a more important part in causing the early death of patients with atrial septal defects than is generally conceded. In the past, the ostium primum type of atrial defect was included under the diagnosis of atrial septal defects. A persistent ostium primum should be suspected when there are signs of mitral insufficiency in addition to those of an atrial septal defect. Incompetence of the mitral and, less frequently, of the tricuspid valves is not unusual with a persistent ostium primum.[14] This combination of lesions presents a much greater stress on the heart than does a simple atrial septal

defect. Uncomplicated atrial septal defect is a rare cause of death in the pediatric age range. In a postmortem series of 176 cases of congenital heart disease recently reviewed, not one example of this disorder was encountered.[15]

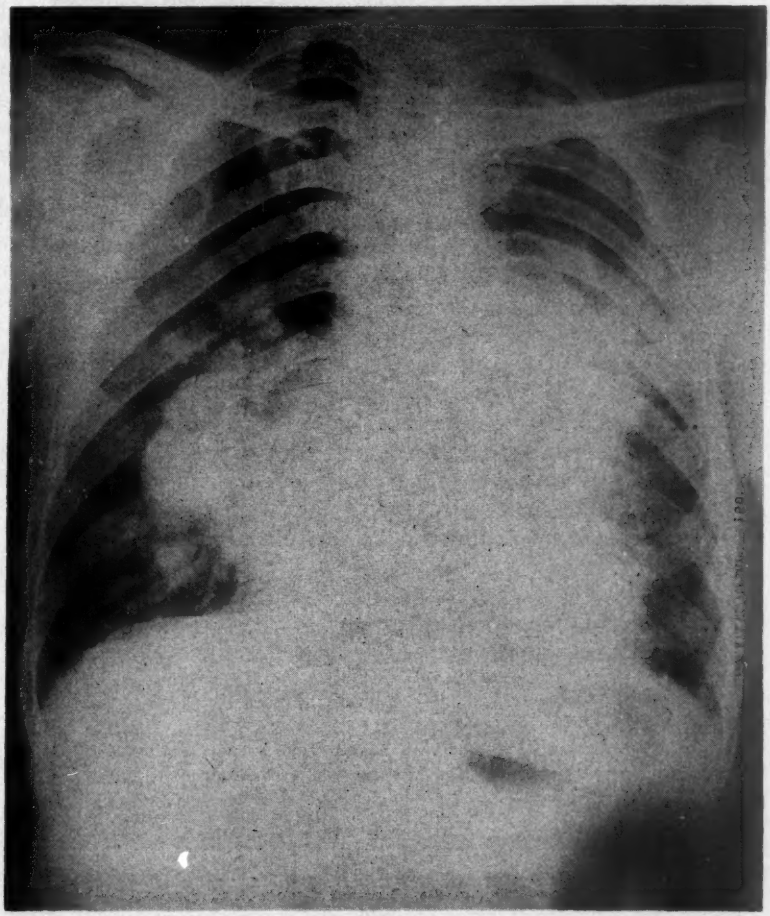

FIG. 7. Posteroanterior film of individual with atrial septal defect, severe pulmonary hypertension, and thrombosis of both main pulmonary arteries.

Respiratory infections are frequent in this disease. This may eventually lead to chronic bronchitis and emphysema, which contribute to the dyspnea of later life.

Pulmonary hypertension is a frequent and major complication of an atrial septal defect. It was present in seven of the 19 subjects in the series, al-

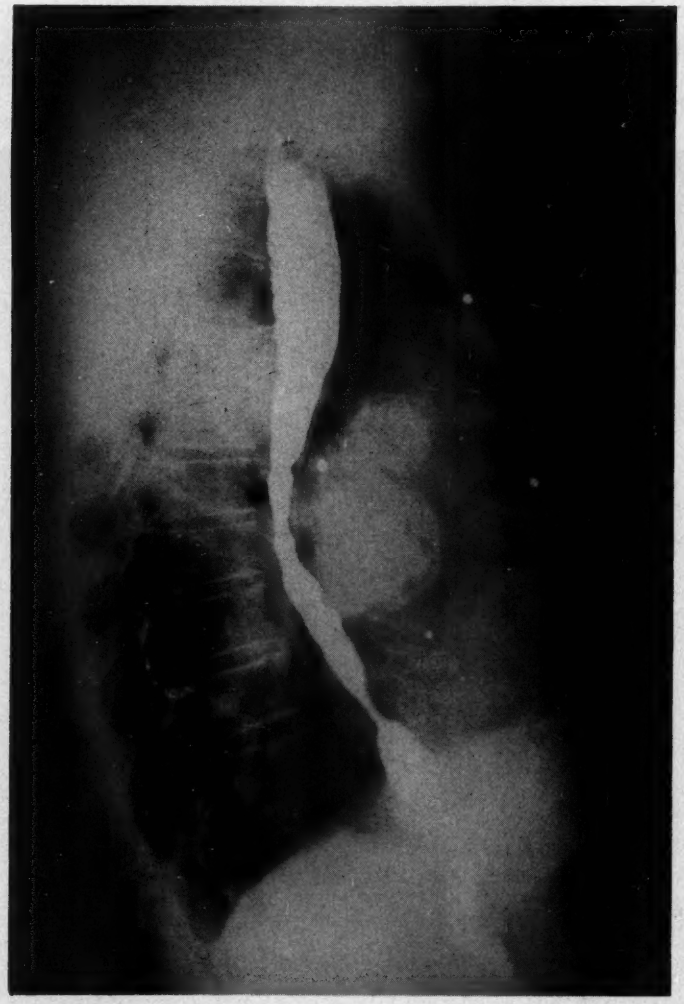

FIG. 8. Lateral film of same patient as in figure 7. Note the massive pulmonary arteries with heavy calcification. Further discussion in the text.

though only four were severely handicapped by it. As pointed out earlier, our two oldest members of this series (both over 70 years of age) had large pulmonary blood flows without an increase in pulmonary vascular resistance. This proves that large flows over a long period of time do not necessarily result in pulmonary hypertension. It would appear that other factors, whether acquired or congenital, are necessary for the development of pulmonary hypertension.

Another serious complication which has occurred in two of our patients was thrombosis of the major pulmonary arteries. Both of these individuals presented evidence of pulmonary hypertension for years preceding the thrombosis. In both the clinical picture was similar. Episodes of chest pain, fever, pleuritic pain and hemoptysis suggested pulmonary emboli and infarction. These episodes, however, developed gradually rather than suddenly, and persisted for weeks. Cyanosis became marked, and clubbing of the extremities was noted later. The chest roentgenogram often showed an exceptionally dense and bulky, comma-shaped shadow in the position of one of the pulmonary arteries. If the process has been present for some time, these structures may be heavily calcified. Figures 7 and 8 are roentgenograms of a man who died shortly afterward. Postmortem examination demonstrated complete occlusion of both pulmonary arteries by thrombosis. The thrombosis of the right pulmonary artery was old, heavily calcified and partially recanalized. A fresh thrombus was present in the main pulmonary and left pulmonary arteries. The small vessels of the lungs were dilated and sclerotic. This patient had a large atrial septal defect. No venous thromboses were found. This man was 65 years of age at the time of death. He had enjoyed vigorous health until the age of 55, when symptoms of pulmonary hypertension developed and signs of reversal of the shunt appeared. The first symptoms of pulmonary thrombosis occurred about one year before death. The subject of pulmonary artery thrombosis has recently been reviewed by Magidson and Jacobson.[16]

Subacute bacterial endocarditis is an extremely rare complication. No patients in this series presented any evidence of subacute bacterial endocarditis in their clinical course.

Cerebral abscesses may result from septic emboli passing through the defect into the systemic circuit if a right-to-left shunt exists. No instance of this complication was recognized in our series.

Summary

Atrial septal defect is the form of congenital heart disease most commonly encountered in elderly subjects. A series of 19 patients over the age of 47 with this disorder is presented. Only three instances of other congenital malformations of the heart were recognized in subjects of the same age range during the period of observation. A long, active life is possible with this disorder. The diagnosis can usually be made without difficulty by clinical examination. Hemodynamic data are presented which suggest that high pulmonary blood flow over a long lifetime does not necessarily result in pulmonary hypertension.

The complications of an atrial septal defect are frequent respiratory infections leading to chronic lung disease, and pulmonary hypertension leading to right ventricular failure and reversal of the shunt. An infrequent but serious complication is pulmonary artery thrombosis.

SUMMARIO IN INTERLINGUA

Defectos del septo atrial es le plus commun forma de congenite morbo cardiac incontrate in subjectos de etate avantiate. Es presentate un serie de 19 patientes con iste disordine, omnes de etates de plus que 47 annos. Durante le periodo del collection del presente serie, solmente tres casos de altere congenite malformationes del corde esseva recognoscite in patientes del mesme periodo del vita.

Un longe e active vita es possibile con iste disordine. Duo membros del presente serie ha etates de plus que 70 annos sed ha nunquam essite impedite per le lesion in lor corde. Infectiones respiratori es commun. Bronchitis chronic e emphysema es frequentemente incontrate in iste patientes de etates avantiate.

Hypertension pulmonar esseva presente in nove del 19 membros del serie. Illo esseva sever in solmente quatro casos. Hypertension pulmonar pote resultar in insufficientia dextero-cardiac con reversion del derivation. In tal casos le prognose es multo adverse. Es presentate datos hemodynamic que demonstra que un forte fluxo pulmonar durante un longe vita non resulta necessarimente in hypertension pulmonar.

Un complication de occurrentia rar in patientes con hypertension pulmonar, con reversion del derivation, e con polycythemia es thrombose del arterias pulmonar principal.

Le diagnose de un non-complicate defecto del septo atrial pote usualmente esser complite—ben que con alicun difficultate—per medio del examine clinic. Le aspectos essential es un elevation systolic supra le dextere ventriculo e arteria pulmonar e un pulmonic murmure systolic con large fissura del secunde sono. La roentgenogramma thoracic revela un allargamento del atrio e del ventriculo dextere. Omne le brancas del arteria pulmonar es dilatate. Le electrocardiogramma exhibi usualmente le configuration de bloco del branca dextere e fibrillation in subjectos de etates plus avantiate.

Quando hypertension pulmonar es presente como complication del tableau de defecto del septo atrial, le systolic murmure pulmonar e le fissura del secunde sono deveni minus prominente. Le principal arteria pulmonar es dilatate, manifeste per un plus pronunciate elevation systolic supra le vaso. Un clic systolic se audi, e P2 es plus forte. Roentgenogrammas thoracic monstra le enorme brancas primari e secundari del arterias pulmonar, sed le brancas tertiari es reducite in lor diametro como signo de hypertension pulmonar.

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BLOOD PRESSURE IN WHITE PEOPLE OVER 65 YEARS OF AGE *

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LITTLE has hitherto been known concerning the range of the blood pressure in "healthy" older people. Analysis of the studies previously made [1] has revealed that the conclusions had been based neither on an adequate number nor on a representative sampling of subjects. The findings frequently were not subdivided according to detailed age groups. The presence or absence of cardiovascular disease had often not been considered. Nor had any systematic effort formerly been made to determine the blood pressure in those who were 90 years of age or older.

Recent statistics have emphasized the importance of investigating the medical problems which beset the aged. The Bureau of Census reported that, in 1955, more than 14,000,000 Americans were 65 years of age or older. The prediction has been made that at least 20,500,000 will be more than 65 years old in 1975.[2] The comparatively large increase in the number of the aged during the first half of this century and the estimated increase in the third quarter are clearly set forth in table 1. The broader aspect of aging becomes quite evident when it is realized that there are now more than 60,000,000 people over 40 years of age in this country.[2] The trend has been generally toward an increased life expectancy. It has been estimated that more than 70% of males who reach the age of 40, and more than 80% of females, will live to be at least 65.[3] Thus, the establishment of normal blood pressure limits in the aged is of importance not only to them but also to younger adults.

The blood pressure in old age has long been a problem, but is assuming even greater importance because of the ever-increasing number of the aged. Questions involving prophylactic care, diagnosis, treatment and insurability constantly arise. Is there a definite, normal range of blood pressure among healthy individuals who are 65 years or older? Does the blood pressure continue to rise with advancing years as it does from birth to 65? [4] Does the blood pressure continue to be higher among women over 65 than among men? Does an increase in the blood pressure after 65 result in a rise in the mortality rate, as before 65? What is the definition of hypertension in the aged? Is 100-plus-the-age a good rule for determining their normal systolic pressure? Is 113 plus one third the age a still better one? Or is 125 plus

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the age best? Does hypertension in the old produce cardiac enlargement, as it does in younger adults? Does it predispose to angina pectoris and acute coronary insufficiency? Is the blood pressure in the aged affected by, or related to, their build and weight? Do geographic location, rural or urban living, ethnic origin, ability to work, and chronic illness significantly affect the blood pressure of the old? What is the blood pressure in healthy nonagenarians? Do the very old who are active, alert and productive have unique blood pressures? Should antihypertensive drugs be employed when the pressure reaches a fixed height?

TABLE 1

Magnitude of Aged Population

Year	Number of Aged*
1900	3,100,000
1925	5,788,000
1950	12,287,000
1975	20,655,000 (estimated)

* Abstracted from U. S. Bureau of the Census, Current Population Reports, Series P-25, No. 123 (Oct.) 1955, p. 8.

The present study attempts to find a solution to some of the many questions and problems which old age raises. Others will be considered in future publications and, hopefully, solved. Still others will demand much further study and research. A short preliminary statistical summary has just been presented.[4c]

MATERIAL FOR THE STUDY

In an attempt to accumulate sufficient data on persons 65 and over, homes for the aged were at first approached, as were large industrial concerns. It was soon found that reliable data on sufficiently large numbers of healthy subjects could not be obtained from these sources. The aid of physicians throughout the country was therefore solicited. Their wholehearted help is hereby gratefully acknowledged. Contact was attempted with that number of physicians in each state which was in direct proportion to the number of its aged inhabitants, and specially planned questionnaires were sent to them (figure 1). Fifteen thousand were obviously carefully completed and returned by approximately 5,000 physicians. Many physicians added pertinent remarks, many others furnished additional data, and some corresponded often with us.

The physicians were asked to choose as subjects for the study those patients, friends or relatives 65 years of age or older who were apparently healthy, in that they were ambulatory, were living in the community, and were able to take complete care of themselves. Those who suffered from certain chronic diseases—e.g., arthritis, cholecystitis, peptic ulcer, uncomplicated diabetes mellitus—were accepted as subjects, but those with cardiovascular disease were excluded. Inmates in homes for the aged were like-

BLOOD PRESSURE STUDY (AGES 65 AND OVER)

INSTRUCTIONS ON REVERSE SIDE

Patient's Initials..... Date Examination.....

Residence: City or Town..... State.....

Color..... Sex..... Age last birthday.....

Ht. (s shoes)..... Ft..... In. Wt. (s shoes or clothing)..... Lbs.

Country of Birth.....

NEW BLOOD PRESSURE OR USE LATEST READING ON LAST PERSON EXAMINED IN APPROPRIATE AGE GROUP

Systolic.....

Diastolic.....

How taken? (circle one) Lying? Sitting?

Prev. maximum blood pressure.....

Physician's name.....

Physician's address.....

.....

CIRCLE ITEMS WHICH APPLY

WORK: Employed full time part time Unemployed Retired

PHYSICAL ACTIVITY: Exceptional Average Less

MENTAL ALERTNESS: Exceptional Average Less

OCCUPATION: (Usual or previous if retired or unemployed)

Farming Professional

Light Manual Heavy Manual Executive, Official or Proprietor

Sales, Clerical, etc. Housewife

HEART DISEASE:

Mild Angina Prev. Angina Hypertensive Ht. Dis. confirmed by

Prev. Coronary Occlusion a. Abn. ECG

Prev. Congestive Failure b. Enlarged Heart

Rheumatic Ht. Dis. Prev. Cerebrovascular Acc.

Mitral Aortic

OTHER CHRONIC DISEASES:.....

.....

REMARKS:.....

.....

PROCEDURE AND INFORMATION DESIRED

SUBJECTS:

THREE PEOPLE 65 YEARS OR OLDER (preferably one each in the age groups 65-75 and 75-85, and 1 above 85) among patients, friends, relatives, in fairly good health and up and about. People able to work are most desirable, although they may have some chronic ailment. However, anyone able to take care of himself is acceptable. If not under active therapy, people with rheumatic heart disease or previous coronary disease may be included, with notation where indicated. Patients on anti-hypertensive medication may be used, but please record only their blood pressure readings prior to institution of this therapy.

PHYSICAL ACTIVITY and MENTAL ALERTNESS should be judged with reference to the status of persons of the same age.

BLOOD PRESSURE RECORDING

The blood pressure should be taken after the patient has rested a few minutes and should be read to the nearest even digit.

The DIASTOLIC PRESSURE should be recorded at complete disappearance of the sound (fifth phase).

WEIGHT AND HEIGHT

Please record the weight of the patient without shoes or clothing; but women may wear a slip and stockings, and men may wear shorts. If they are weighed with more clothes, subtract the few pounds the clothes weigh.

Height should be recorded in stocking feet. If patients keep their shoes on, subtract the height of the heel.

The results of this investigation will be published in the usual medical channels.

If you desire additional forms, write to Arthur M. Master, M.D., Director, Blood Pressure Study, 11 East 100th Street, New York 29, N. Y.

FIG. 1. Questionnaire card sent to physicians, showing data requested for each patient and summary of general instructions. A letter with detailed instructions and explanation of the purpose of study accompanied this card.

wise excluded, since the proportion of sick persons among them is higher than it is among the generality of old people.

Of the 15,000 older subjects who had been examined by physicians throughout America, 5,757 were considered by us to be apparently healthy, as defined above, and form the basis of this report. Of these, 2,998 were men and 2,759 were women. The blood pressure readings were first analyzed for internal homogeneity, since they came to us mainly from six different sources: (1) individual general practitioners; (2) members of The American College of Physicians; (3) members of the American Heart Association; (4) physicians employed in various Union Health Centers; (5) members of the American College of Chest Physicians, and (6) physicians on the staff of the Veterans Administration. The mean blood pressure and the standard deviation found in the subjects from each of these sources were separately calculated and then compared. They were found to be remarkably similar, and therefore the blood pressure readings of all sources were combined for analysis.

The geographic distribution of the subjects was proportionate to that of white persons 65 years of age and over,[5] except for a slight over-representation of subjects from the northeastern states. However, since the mean values and standard deviations found in the six customary geographic areas of the United States were similar, it was not considered necessary to "weight" the data. Our sample population included subjects from various ethnic and economic groups, and subjects from urban and rural communities. The proportion of subjects working or retired was found to be similar to that of the aged population of the country.[6] This was to be expected, since the reporting physicians were scattered throughout the country, and treated all the different types of people who, together, make America.

For these reasons, this report on the blood pressure in the aged is the first to be based on data obtained from a large group of active, apparently healthy white persons. It was not intended to be a random sample of the entire aged population, such as would be obtained if every tenth old person, including the sick, had been studied. Data so gathered would not, it was felt, help to establish the normal limits of the blood pressure in the active, apparently healthy aged. The blood pressure in old people with heart disease and in those who are in institutions is now being studied separately.

The blood pressures recorded and analyzed in this study were "casual" readings. In order to minimize emotional pressure fluctuations, the physicians were advised to allow the subject to relax for a short period, and to put him at ease. We clearly indicated our preference for a new blood pressure reading, which the doctor was urged to chart to the nearest 2 mm. Hg. If, however, a reading was taken from a record, it was the most recent one.

Figure 1 is a reproduction of the questionnaire, with the data on the obverse and the directions on the reverse. A letter describing our purposes and giving detailed directions was also enclosed. The age of the subject

was recorded as that on the nearest birthday. The height was measured with the subject unshod, the weight with only undergarments on. The blood pressure was taken in the sitting position; the systolic was recorded at the commencement of Korotkoff's sound, and the diastolic at its complete disappearance, i.e., the fifth phase. This is in accordance with the 1951 recommendations of the American Heart Association.[7]

Other pertinent information was gathered: the state of residence of each subject, the size and nature of the community, the country of birth, the past or present occupation whether employed or retired, the amount of physical activity engaged in, and the mental alertness evinced. The information thus gathered from the questionnaire was put into code form and transferred to punch cards for machine tabulation and analysis.

Statistical Analysis

From the raw data thus accumulated, arithmetic means, standard deviations * and median and modal values were obtained for each sex in each five-year age group of subjects. Subjects who were 95 years of age or older were considered in one age group. The statistical reliability of the differences between mean values was calculated from a computation of the standard error of the respective means. Frequency distribution graphs for systolic and diastolic pressure were then made by sex for each five-year age group. It was noted that physicians tend to record the blood pressure readings at the nearest zero figure (130–140–150). This resulted in peaks at readings whose terminal digit was zero, instead of smooth curves of values between the extremes of the distribution curve. This was observed first by Janeway,[1b] and has been found in other large surveys.[8] To minimize this artefact, 10 mm. Hg class intervals were adopted, in the center of which were placed the blood pressure readings ending in zero. Thus, the systolic class intervals ranged from 85–94 up to 245–254, and the diastolic intervals from 45–54 up to 125–134. All readings below 85 mm. Hg systolic and below 45 mm. Hg diastolic were placed in a single class interval. The frequency was expressed as a percentage.

Results

A. Mean (Average) Pressure: Table 2 and figure 2 show the mean systolic and diastolic pressures of each sex in each five-year age group. Unlike the trend found in subjects under the age of 65, the *mean systolic and diastolic pressures do not rise continuously with age after 65.* In males, the mean *systolic* rises only slightly (2 to 3 mm.), to 146 mm. Hg, between the 65–69 years and in the seventies; thereafter, it is virtually stationary. In females, the mean systolic rise is greater (5 mm.), to 159 mm., between the

* Standard deviation is the usual measure of the spread of the data. It is equivalent to about the middle 68% of the observations. Hereafter, the Greek symbol σ will be used to represent the standard deviation.

TABLE 2

Mean Blood Pressure of Apparently Healthy Aged People, 65–106 Years

Age Group	No. Cases	Systolic ±1 Standard Deviation	Diastolic ±1 Standard Deviation
Males			
65–69	911	143 ± 26.0	83 ± 9.9
70–74	694	145 ± 26.3	82 ± 15.3
75–79	534	146 ± 21.6	81 ± 12.9
80–84	385	145 ± 25.6	82 ± 9.9
85–89	325	145 ± 24.2	79 ± 14.9
90–94	124	145 ± 23.4	78 ± 12.1
95–106	25	145 ± 27.5	78 ± 12.7
Total	2998	145 ± 22.3	82 ± 10.0
Females			
65–69	856	154 ± 29.0	85 ± 13.8
70–74	682	159 ± 25.8	85 ± 15.3
75–79	464	158 ± 26.3	84 ± 13.1
80–84	344	157 ± 28.0	83 ± 13.1
85–89	263	154 ± 27.9	82 ± 17.3
90–94	122	150 ± 23.6	79 ± 12.1
95–106	28	149 ± 23.5	81 ± 12.5
Total	2759	156 ± 28.0	84 ± 14.7

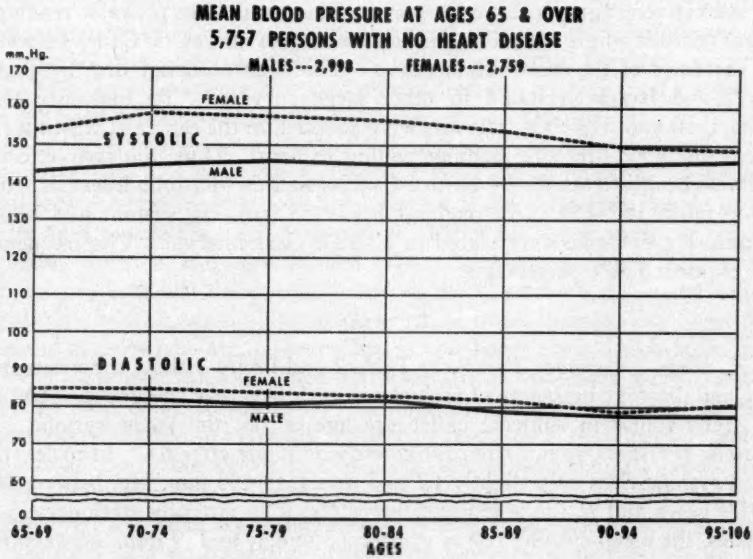

FIG. 2. Note (1) blood pressure does not rise continuously after 65, (2) female systolic pressure is higher than male, (3) diastolic pressures are similar. Pulse pressure of women therefore is wider.

65–69 years and the 70–74 years; thereafter, it decreases steadily. After the age of 90 it is below the average found in the 65–69 year group. The systolic pressures in both sexes thus approach each other in extreme old age, though that in the female is always slightly higher.

The *average diastolic pressure* in both sexes shows little variation between the ages of 65 and 80, and thereafter declines slightly. It is highest in the 65–69 year age group in men (83 mm. Hg), and in the 65–74 year age group in women (85 mm. Hg). At the age of 95 it is 78 mm. Hg in

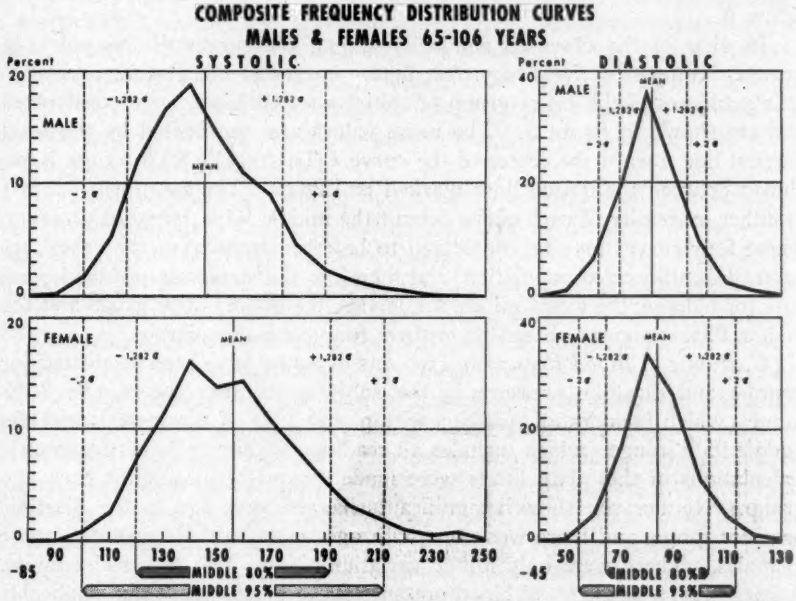

FIG. 3. These curves represent the total apparently healthy sample population. The central solid vertical line in each curve represents "mean" pressure; the dotted vertical lines mark the limits of the middle 80% range. Note characteristic bell-shaped pattern. The sex difference is apparent, females manifesting higher mean values and wider middle 80% and 95% ranges of pressure. (σ = Standard deviation.)

men and 81 mm. Hg in women. The average in women is higher than it is in men in each age group, but the difference is too small to be of practical significance.

The mean blood pressure of the entire sample population was found to be 145/82 mm. Hg in men and 156/84 mm. Hg in women. Women thus have a definitely higher systolic pressure but only a slightly higher diastolic. The modal pressure (the highest frequency of any pressure) is 140/80 in both sexes; this figure reflects the tendency of physicians to record their readings at the nearest zero figure. The pulse pressure in all the age groups combined is greater in women (72 mm. Hg) than in men (63 mm. Hg).

B. Analysis of Frequency Distribution Curves: Frequency distribution curves of the systolic and diastolic pressure were constructed for each sex in each five-year age group.[4c] A comparative analysis showed that the contours of the curves, the mean values, the modes (peak or highest incidence), and the middle 80% range for each sex were similar throughout this entire age range. All had the basic bell-shaped pattern characteristic of many biologic phenomena; in common with some of them, the blood pressure curves were somewhat skewed to the right, i.e., not perfectly symmetric about the mean but with a wider range of values above the mean than below it.

In view of the observed similarity among the curves of five-year age groups, "composite" frequency distribution curves of the systolic and diastolic pressures of the entire group of subjects for each sex were constructed and are shown in figure 3. The mean values are represented by the solid vertical line toward the center of the curve. The middle 80% range is included between the dotted lines marked $\pm 1.282\sigma$. The two lines ($\pm 2\sigma$) at either extremity of each curve delimit the middle 95% range of pressure. These four curves may be considered to be representative of the entire apparently healthy aged population, and therefore the standards of blood pressure for old age, the mean values, the modes, the middle 80% range and the middle 95% range are based upon these four composite curves.

C. Range of Blood Pressure: Two sets of limits have been calculated for systolic and diastolic pressure in the subjects studied: the middle 80% range (which includes all readings within $\pm 1.282\sigma$ of the mean), and the middle 95% range (which includes all readings within $\pm 2\sigma$ of the mean). Calculations of these two limits were made separately by sex for each age group. Neither sex showed significant changes with age in the diastolic pressure range, and there was none with age in the systolic pressure range in males. There were only minor variations in the female systolic limits. Accordingly, a single set of blood pressure standards for each sex, applicable to all persons 65 years of age or older, has been computed from the data and is proposed for general use. The blood pressure values have been adjusted very slightly to the figures customarily used by physicians in recording blood pressures. On this basis, the middle 80% range for males is 115–175/70–95; for females, it is 120–192/65–102. The middle 95% range for males is 100–190/62–102; for females it is 100–212/55–112.

Discussion

This study reveals an important difference in the behavior of the blood pressure of apparently healthy older and younger persons. The vast majority of investigators has found that blood pressure rises continuously from birth until the 60–65 years.[4a, b] The present investigation indicates that the systolic pressure does not continue to rise with age after the seventy-fifth year, or the diastolic after the seventieth.

One may speculate on the reasons for this cessation of the rise in blood pressure after the 70–74 years. It is possible that the factors which result in a progressive increase in the pressure in earlier years exert a diminishing effect later in life. These factors are the gradual replacement of elastic tissue in the arterial wall by collagen, and the development of atherosclerosis which, by reducing the distensibility or elasticity of the arterial tree, elevates the blood pressure.[9, 10] It is possible, too, that many people with a relatively or actually high blood pressure do not develop evidence of cardiac or cerebrovascular disease until the advanced ages, say, past 70. At this age these diseases finally do become apparent with greatly accelerated frequency, or death occurs. The net effect is to maintain a constant mean pressure in men and a declining mean pressure in women after the sixty-fifth year. Of course, there are many exceptions to this trend; it is not uncommon for persons with quite high blood pressures to survive to advanced ages, often without significant disability.

It is always well to remember that a blood pressure reading is only one part of the examination and should be evaluated in the light of the entire clinical picture. In presenting two standard ranges of blood pressure in the apparently healthy aged, the middle 80% and the middle 95%, we do not intend to indicate that a blood pressure falling within the former range is always normal, or that one falling beyond the latter range is always serious. Actually there is no sharp demarcation line between a "normal" and an "abnormal" blood pressure, for they often overlap. The same blood pressure may be found in one person without any cardiovascular abnormality, whereas in another it may be associated with cardiac enlargement or other evidence of hypertensive cardiovascular disease. The middle 80% and 95% standard ranges here presented are therefore arbitrary. Nevertheless, we believe that these ranges have a practical importance for the physician, since they indicate in general that persons whose blood pressure falls within the middle 80% but who have no evidence of hypertensive cardiovascular disease do not require antihypertensive therapy. It should be recalled that subjects with heart disease have been excluded from this study.

We do not wish to imply that persons with a blood pressure near the upper limits of the middle 80% range, e.g., 174/94 in a male, will, on the average, have the same life expectancy as those with a lower blood pressure, e.g., 122/82. Statistics compiled by insurance companies [11a, b] and others [12] indicate that there is a rise in mortality with an increase in blood pressure in the age range up to 70 for which life insurance companies have information. However, some distinction must be made between the observations and clinical interpretation of physicians on the one hand, and the findings and practices of insurance companies on the other. Insurance companies are concerned with the increased mortality that relatively small differences in blood pressure may produce, and which may necessitate substantially higher premium rates. Thus, the difference between a systolic pressure of 120 and

146 may have no significance to the physician; to insurance companies, however, such a difference may have a material adverse financial effect as a result of a significant difference in long-range survival. Their criteria are based on the observed mortality in large groups classified according to blood pressure levels. All persons falling within a group are treated alike. In contrast, the physician considers each individual per se. He knows that many people, particularly women, are very adaptable to their blood pressure, and tolerate even high levels extremely well. Symonds [1e] and Lew [13] have emphasized this fundamental difference between the individual and the mass approach.

To adopt blood pressure standards for the aged below those of the majority of apparently healthy people would expose many older persons to unnecessary psychologic trauma and subject them to unnecessary treatment. The physician must consider the blood pressure in relation to the entire clinical picture, and must decide on the need for treatment in each case.

There can be little doubt that a blood pressure beyond the middle 95% range is abnormal and may be considered hypertensive. The evaluation of blood pressures falling between the upper limit of the middle 80% range and that of the middle 95% range depends entirely on the clinical findings.

The findings of Bechgaard [14] tend to confirm our own—that elderly people whose pressure lies beyond the 95% limits are generally abnormal. In a follow-up study (up to 19 years) of 1,000 Danes treated in the Outpatient Department of the University Clinic at Copenhagen, the subsequent mortality among those with systolic pressures in excess of 200 mm. Hg and of diastolic pressures in excess of 120 mm. Hg at first observation was much higher than among those with pressures under that level, even among those who were 60 or over at first observation.

The blood pressures upon which this study was based were "casual" readings. There is some difference of opinion concerning the clinical validity of such readings. It has been argued that the "basal" pressure is of greater value, but it requires repeated readings with the subject at complete rest and is thus very time-consuming. It is our opinion that the "casual" pressure is of greater practical importance, for it reflects the reaction of the individual to the environment to which he is exposed. Our understanding of the relationship between blood pressure and morbidity and mortality is based almost entirely on "casual" pressure figures.

The lability of the blood pressure produced no significant error, as indicated by the smooth character of the frequency distribution curves of blood pressure found in our study. The large number of readings militated against this factor. It is probable also that most physicians carefully followed our instructions when taking the blood pressure.

Sex Difference: In this study of persons over 65, both the systolic pressure and the pulse pressure were found to be higher among women than men. This sex difference first appears at about the age of 45,[4a, b] approxi-

mately the age of the menopause, and increases progressively until the 70–74 years. The difference is great enough to necessitate having separate standards for each sex. Although women have a higher systolic pressure, they tolerate it better than men, and their life expectancy is greater. After the ninetieth year, when the life expectancy is approximately the same for each sex, the mean systolic pressure of women falls and approaches that of men. Has the degree of atherosclerosis become the same in both sexes at this advanced age? This is suggested by the observation of Ackerman and Dry, who noted a rise in atherosclerosis in women between the seventh and eighth decades comparable to that which occurs in men between the fifth and sixth decades.[15]

Nothing at present satisfactorily explains the circulatory dynamics which result in the higher systolic pressure and greater pulse pressure in women. The factors which enable women to tolerate higher pressures better than men are unknown. The reason for hypertension being so much more benign in women is an important area for future research, as it is probably intimately related to the entire problem of sex difference and atherosclerosis. Although women in the 50-to-70 year age range seem to have higher blood levels of free, esterified and total cholesterol, total lipids, lipid phosphorus, neutral fat and S_f 10–20 Gofman lipoproteins, they have a lower incidence of atherosclerosis, particularly of the coronary arteries. There is also a steady rise in serum cholesterol and S_f 10–20 lipoprotein molecules in women up to and after the age of 65.[16] Master's observation that true hypertension was a factor in 75% of the cases of coronary occlusion in women under 65 years of age but in only 25% of the cases in men [17] must be confirmed in the older age groups. We are thus confronted by an apparent paradox: older women have a higher blood pressure and higher serum lipid values, both of which are said to shorten life, yet they live longer.

Summary and Conclusions

The establishment of blood pressure limits in old age has now become important, since the number of persons over 65 years is already so large and is steadily increasing. Answers to many questions concerning the relationship between the blood pressure reading and its possible clinical significance must be found. This report presents the results of the first valid study of the blood pressure of an adequate number (5,757) of apparently "healthy" white men and women 65 years of age and older in the United States.

The frequency distribution curves of the blood pressure show that the factor of lability of pressure was not a source of error in our large group. When the number of subjects is large enough, and when the blood pressure is taken with reasonable care, the lability of the arterial pressure hardly influences the results.

After the age of 65 the blood pressure does not show a consistent rise with advancing years, as it does below the age of 65. The *mean systolic*

pressure in both sexes continues to rise slightly until the 70–74 years, when the highest level of the mean systolic pressure is reached (159 mm. Hg among *women*). After the age of 74 the systolic pressure in women declines slowly for 10 years; it falls more definitely after the age of 85, reaching the lowest level in the 95-year group (149 mm. Hg). The average systolic pressure in *men* remains essentially constant—145 mm. Hg after the 70–74 years. The *sex difference* is greatest in the 70–74 year group, when the systolic pressure in women is 14 mm. Hg higher than it is in men. The lowest sex difference (5 mm. Hg) is found after the age of 95. Thus, the systolic pressures of both sexes approach each other in extreme old age, but always remain slightly higher in the female.

The *diastolic blood pressure* is practically constant after the age of 65 in both sexes, with minor exceptions; it is highest in the 65–69 year group, and is very slightly higher in women: in men, the mean is 83 mm. Hg, in women, 85. After the age of 69, the diastolic pressure declines slightly but continuously, falling to 78 mm. Hg in men, and to 81 in women after the ninety-fifth year. This difference of 2 to 3 mm. Hg is not of practical significance.

The mean blood pressure for all the subjects, 65 to 106 years of age, was found to be 145/82 mm. Hg in men and 156/84 mm. Hg in women. The "modal" blood pressure (the peak or highest frequency of any pressure) was 140/80 mm. Hg in both sexes. The pulse pressure is larger in women than in men at all ages: 63 mm. Hg among all males, 72 mm. Hg among all females.

Two ranges of blood pressure have been computed for each sex between the 65th and 106th years. The *middle 80% range* in males is 115–175/70–95, and in females is 120–192/65–102. In general, if blood pressures fall within these limits and are not associated with evidence of hypertensive heart disease, antihypertensive drug therapy is not indicated. The *middle 95% range* in males is 100–190/62–102, and in females is 100–212/55–112. A blood pressure reading beyond these figures is practically always abnormal. The ranges suggested should be used only as clinical guides. The final evaluation of each blood pressure reading depends on the entire clinical picture. This is particularly true for blood pressures falling near or beyond the upper limit of the middle 80% range.

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Summario in Interlingua

Iste reporto presenta le resultatos del prime valide studio del pression de sanguine in un adequate numero (5.757) de apparentemente normal masculos e femininas de racia blanc, habitante le Statos Unite e habente attingite etates de 65 annos o plus.

Le curvas de distribution del frequentias de pression de sanguine monstra que le factor del labilitate del pression non esseva un fonte de errores in nostre grande gruppo.

Post le etate de 65 annos, le pression del sanguine non exhibi un ascendita continue in correlation con le avantiamento del etate, como il es le caso infra le etate de 65 annos. Le *pression systolic medie* in ambe sexos continua montar levemente usque al nivello de etate de 70 a 74 annos quando le plus alte valor pro le pression systolic medie es attingite (159 mm de Hg inter *feminas*). Post le etate de 74 annos, le pression systolic in feminas descende lentemente durante un periodo de 10 annos. Illo descende plus marcatemente post le etate de 85 annos e attinge su plus basse nivello in le gruppo de un etate de 95 annos (149 mm de Hg). Le pression systolic medie in *masculos* remane essentialmente constante post le nivello de etate de 70 a 74 annos (145 mm de Hg). Le differentia inter le sexos es maximal in le gruppo de etates de 70 a 74 annos. A iste tempore le pression systolic in feminas es 14 mm de Hg plus alte que in masculos. Le differentia inter le sexos attinge su minimo (5 mm de Hg) post le etate de 95 annos. Assi le pressiones systolic pro le un e le altere sexo converge a altissime etates, sed le valores pro feminas remane semper levemente plus alte.

Le *pression de sanguine diastolic* es practicamente constante in ambe sexos post le etate de 65 annos. Le exceptiones a iste regula es minor. Iste pression es le plus alte in le gruppo de etates de 65 a 69 annos; illo es levissimemente plus alte in feminas. In masculos, le valor medie es 83 mm de Hg; in feminas, 85. Post le etate de 69 annos, le pression diastolic descende leve- sed continuemente. Illo attinge un minimo de 78 mm de Hg in masculos e de 81 mm de Hg in feminas post le etate de 95 annos. Iste differentia de 2 a 3 mm de Hg ha nulle signification practic.

Le pression de sanguine medie pro omne le subjectos, con etates de ab 65 usque a 106 annos, esseva 145/82 in masculos e 156/84 in feminas. Le pression "modal" (le culmine o frequentia maximal del pression) esseva 140/80 in ambe sexos. Le pression de pulso es plus grande in feminas que in masculos a omne etates. Illo es 63 mm de Hg inter omne le masculos e 72 mm de Hg inter omne le feminas.

Duo scalas de pression de sanguine esseva computate pro cata un del duo sexos a etates de inter 65 e 106 annos. Le *scala pro le 80% intermediari* es 115–175/70–95 in masculos e 120–192/65–102 in feminas. In general, si le pression de sanguine se mantene inter iste limites e non es associate con signos de hypertensive morbo cardiac, nulle medication antihypertensive e nulle altere therapia es indicate. Le *scala pro le 95% intermediari* es 100–190/62–102 in masculos e 100–212/55–112 in femininas. Pressiones de sanguine al exterior de iste limites es practicamente semper anormal. Le scalas hic presentate deberea esser usate solmente como guida clinic.

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PITFALLS IN THE DIAGNOSIS OF PHEOCHROMOCYTOMA *

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THE clinical course of patients with tumors secreting epinephrine and norepinephrine is subject to great variations and may often simulate in every aspect the course of patients with essential hypertension. At the present time it is widely recognized that the diagnosis of pheochromocytoma must be considered in the evaluation of every patient with significant hypertension. The importance of establishing the diagnosis is great because of the curability by surgical removal and the possibility of malignant degeneration in the tumor. Two of 12 cases of pheochromocytoma were malignant in our series.[2] Only 13 verified pheochromocytomas have been found on exploration or autopsy in the last 10 years at the Lahey Clinic. Poppen has carefully explored the adrenal glands in approximately 1,200 splanchnicectomies for hypertension in this clinic and has never found a pheochromocytoma. Smithwick [11] has found pheochromocytoma in 0.5% of hypertensive patients whose adrenal glands were explored at splanchnicectomy.

CLINICAL ASPECTS IN 13 CASES OF PROVED PHEOCHROMOCYTOMA

In this study two groups of patients have been reviewed, the first a group of 13 patients with pheochromocytoma, the second a group of 75 consecutive patients with hypertension screened for pheochromocytoma as part of the evaluation of their hypertension.

The group of 13 cases of pheochromocytoma, all proved by surgical excision or autopsy, were seen from 1946 to 1955. Four of these were reported in detail by Bartels and Cattell [1] in 1950. Four of the 13 patients have died. We have been in contact with all nine of the survivors within the last year. There were six women and seven men, whose ages ranged from 20 to 57 years. The ages at onset of symptoms attributable to pheochromocytoma ranged from nine to 51 years.

Ten patients had classic attacks consisting of palpitation, sweating, flushing or blanching, vertigo, headache, dyspnea, chest pain or tremor. The other three patients had no typical signs, and pheochromocytoma was not suspected until the diagnosis was established at operation or autopsy. One died during lumbar sympathectomy for arteriosclerosis obliterans

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associated with diabetes mellitus; death was due to pulmonary edema in his only known attack of hypertensive crisis attributed to excessive activity of the pheochromocytoma. The second patient with unsuspected pheochromocytoma had a diagnosis of Cushing's disease, and the surgically removed adrenal gland showed both pheochromocytoma and adrenal cortical hyperplasia. The third patient had no symptoms except for abdominal swelling; a huge cystic tumor filled the entire abdomen. The pathologic diagnosis was pheochromocytoma.

Pheochromocytoma was diagnosed before operation by routine screening of 10 of 11 patients who had known hypertension. One of the remaining two patients who were never found to have elevated blood pressure described classic attacks which led to the diagnosis.

Pheochromocytoma with Associated Diabetes in Nine of 13 Cases

Eight patients had diabetes mellitus when first seen. In one patient, who had metastatic pheochromocytoma, diabetes mellitus developed after the original tumor was removed. One of the diabetic patients had attacks for 16 years which were thought to be insulin reactions, but in retrospect, some of these undoubtedly represented hypertensive crises. Four of the 13 patients with proved pheochromocytoma had hypertension but no diabetes. Two had diabetes with paroxysmal hypertension, and seven had sustained hypertension and diabetes.

Pheochromocytoma with Hypermetabolism in Five of 13 Cases

In addition to paroxysmal attacks, constant hypertension and diabetes, a fourth common feature of the clinical picture is a hypermetabolic state, a condition that may easily be confused with thyrotoxicosis. Reports of basal metabolic rates were available in four cases; in three the rates were distinctly increased, ranging from plus 30 to plus 90. One of the four patients with an elevated basal metabolic rate (plus 26) underwent thyroidectomy for a nontoxic thyroid adenoma 14 months after removal of the pheochromocytoma. A fifth patient, on whom no diagnostic studies relative to thyroid function were available, had undergone thyroidectomy before coming to the Lahey Clinic. All five of the hypermetabolic patients had both diabetes and sustained hypertension. It is noteworthy that four of the 13 cases of pheochromocytoma were referred from the thyroid section of the clinic for diagnostic study.

Regitine as a Screening Test in 75 Cases of Hypertension

During the years of this study we have used a number of pharmacologic diagnostic tests, including provocative tests with Mecholyl, histamine or Etamon, and adrenergic blocking tests using Regitine and Dibenamine. The very number of available tests is evidence of the lack of reliability of any one

of them. This is probably a result of the nature of this group of tumors, which vary widely in their chemical activity, both quantitatively and qualitatively. Goldenberg [7, 8] et al. in 1950 reported studies on the content of epinephrine and norepinephrine (arterenol) in a group of these tumors, indicating a wide variation throughout their series. Although we have not done similar studies, we suspect that one of our patients with no characteristic attacks, no diabetes and only mild hypertension had a tumor which had no significant amount of adrenergic activity. In a number of reports in the literature of the last several years [1, 3-9, 11] the reliability of these pharmacologic tests has been discussed.

For the screening of hypertensive patients for suspected pheochromocytoma at the Lahey Clinic we are now using primarily one provocative test, Mecholyl, subcutaneously, and one blocking test, Regitine, intravenously, because we believe these are the most useful tests now available and because we hope to obtain a more accurate idea of the reliability of these tests by employing a uniform technic. The histamine test is used less frequently because in our hands it has provoked too many false-positive reactions.[5] The rarity of the tumor adds to the difficulty of obtaining significant statistical studies.

In recent months we have had one technician perform Regitine tests on all our patients undergoing a routine survey for evaluation of hypertension. We have reviewed a series of 75 consecutive Regitine tests and have attempted to evaluate their reliability.

In these 75 cases there were no positive tests, using as a criterion for positive indication of pheochromocytoma a fall of 35 mm. or more in the systolic pressure and a fall of 25 mm. or more in the diastolic pressure after a dose of 5 mg. of Regitine was administered intravenously. The effect should appear within two minutes and need not persist for more than two and a half minutes.

In seven tests there was a significant fall in one reading, but not in both systolic and diastolic pressures.

Assuming that none of these 75 patients had a pheochromocytoma, we can conclude that there were no false-negative tests in this small series. To check this assumption we reviewed these records. In 44 cases, tests were made as part of routine examinations for hypertension. None of the 44 had a history of paroxysmal attacks suggesting pheochromocytoma. A negative test was thought to constitute adequate screening for such cases. In the remaining 31 cases the diagnosis of pheochromocytoma was suggested by one or more observers because of paroxysmal attacks. Eight of these patients had diabetes mellitus, and three had hypermetabolic conditions, with basal metabolic rates greater than plus 20. Intravenous pyelograms, done on 14 patients, showed evidence of masses in the suprarenal area in three. Pheochromocytoma was subsequently excluded by adrenal biopsy in one case and by presacral pneumogram in another. One patient failed to return

for a recommended pneumogram and has not had further follow-up study. A total of seven presacral retroperitoneal pneumograms and two aortograms was done. All were negative for adrenal tumors. Four of this group had surgical explorations of the adrenal region, three in connection with splanchnicectomies and one simply for adrenal biopsy. Subtotal adrenalectomy was carried out at the time of splanchnicectomy in one patient. All four of these procedures were negative for adrenal tumors.

False-Positive Regitine Test Produced by Rauwolfia

An interjection should be made at this point. It was brought to our attention during the course of this study that the Rauwolfia products might interfere with the reliability of the Regitine test. This fact is important because so many of our more recent patients who were sent to the clinic for study had already taken one of these drugs. For this reason we reëvaluated the Regitine test in light of previous Rauwolfia therapy.

Table 1 lists a series of 10 patients (none of whom was included in the original series) who were on Rauwolfia when subjected to a Regitine test and all of whom had suggestive positive results. Only three, however, had strictly positive results as indicated by a 35 mm. drop in the systolic and a 25 mm. drop in the diastolic pressure (cases 93, 95 and 96). Six patients had symptoms strongly suggestive of a pheochromocytoma. As can be seen from the last column in table 1, every possible method of proving or disproving the diagnosis was utilized in these six patients. In cases 90 and 96 a bilateral adrenal exploration and biopsy were undertaken, since the patients' symptoms and Regitine tests were suggestive of pheochromocytoma, but proved to be negative. Case 93 also had many pertinent symptoms and died suddenly while being prepared for surgery. Autopsy was negative for tumor. The Regitine test was so dramatically and markedly positive in case 95 that an exploratory operation was carried out, but was negative.

It can be deduced, therefore, that for the Regitine test to be of significant diagnostic value the Rauwolfia product must be withheld for a period of at least one month. Plummer,[10] of the Ciba Laboratories, has stated that animal experiments at Ciba Pharmaceutical Laboratories have shown evidence that Rauwolfia was still present as long as a month after the drug was withdrawn. Phenobarbital has also been noted to have the same effect as Rauwolfia.[12]

Difficulty in the Diagnosis of Pheochromocytoma

Case 90 is an example of the pitfalls in the diagnostic study for pheochromocytoma. This patient had had sustained hypertension for many years, with innumerable attacks of palpitation, headache, dizziness and weakness. Angina precluded the use of provocative tests. The urinary catechol test for epinephrine showed a high titer in the usual range for pheochromo-

TABLE 1

Positive or Strongly Suggestive Positive Regitine Tests That Proved to Be False

Case	Drug	Pressure Grading	Regitine Test	Other Procedures
89	Serpasil, .12 mg. t.i.d.	2	152 116 −36 —— → —— —— 94 72 −22 Depressed 20 min. +	Retroperitoneal pneumogram negative I.V. pyelogram negative 24 hr. urine epinephrine normal
90*	Raudixin, 100 mg. b.i.d.	2	196 178 −18 —— → —— —— 112 102 −10 Back to previous in 20 min.	24 hr. urine epinephrine elevated to 640 mg. Aortogram negative Presacral retroperitoneal pneumogram positive Cold pressor 204/114 → 226/116 Exploration for pheochromocytoma negative Adrenocortical tumor found; postoperative death
91*	Raudixin, 50 mg. t.i.d.	2	194 160 −34 —— → —— —— 114 100 −14 Depressed 20 min.	Retroperitoneal pneumogram negative I.V. pyelogram negative Histamine provocative test negative
92	Raudixin, 50 mg. b.i.d.	2	250 210 −40 —— → —— —— 140 120 −20 Depressed 20 min.	24 hr. urinary epinephrine normal
93*	Serpasil, .25 mg. q.i.d.	1	218 180 −38 —— → —— —— 160 80 −80 Depressed 20 min.	Died during preparation for surgery Autopsy negative for pheochromocytoma
94	Serpasil, .25 mg. t.i.d.	1	152 130 −22 —— → —— —— 98 76 −22 Depressed 16 min.	24 hr. urinary epinephrine 240 mg., 138 mg. Pneumogram negative Mecholyl provocative test negative
95	Raudixin, 50 mg. t.i.d.	2	186 128 −58 —— → —— —— 100 72 −28 Depressed 14 min.	Mecholyl provocative test negative Presacral pneumogram negative Abdominal exploration negative
96*	Ansolysen, 20 mg. b.i.d. Reserpine, .1 mg. t.i.d.	2	236 198 −38 —— → —— —— 142 116 −26 Depressed 4 min. only	Exploration and biopsy of adrenal negative Bilateral sympathectomy: good response
97*	Apresoline, Raudixin, 50 mg. q.i.d.	2	280 230 −50 —— → —— —— 144 122 −22 Depressed one-half hr. Repeat test in hospital negative	I.V. pyelogram negative Cold pressor elevation of 20/30
98*	Sandril, .25 mg. t.i.d.	1	172 148 −24 —— → —— —— 124 104 −20	Mecholyl provocative test negative Histamine provocative test negative Cold pressor elevation of 30/24 24 hr. urinary epinephrine normal

* Symptoms strongly suggestive of a pheochromocytoma.

cytoma, as may be the case if anxiety has stimulated normal adrenal glands. The presacral retroperitoneal pneumogram revealed a tumor on the superior surface of her one remaining kidney. Her right kidney had been removed for abscess many years before. Exploration for pheochromocytoma was negative. Death was attributed to a lower nephron nephrosis caused by the opaque dye used for the aortogram. The positive pneumogram was explained by an innocent adrenocortical adenoma.

TABLE 2
Results of Regitine Tests

	True Positive	True Negative	False Positive	False Negative
Present Study (79 Cases)				
Pheochromocytoma	2	—	—	2
No pheochromocytoma*	—	75	0	—
Total	2	75	0	2
Reported by Gifford et al.[6] (114 Cases)				
Pheochromocytoma	7	—	—	0
No pheochromocytoma†	—	103	4	0
Total	7	103	4	0

* Patients without previous sedatives, including Rauwolfia.
† False-positive reactions attributable to sedation before test.

CLINICAL SYNDROMES WITH PAROXYSMAL OR SUSTAINED HYPERTENSION SIMULATING PHEOCHROMOCYTOMA

Evans et al.[5] have enumerated some of the conditions which mimic pheochromocytoma, the most common being anxiety or hysteria states, often with hyperventilation. Other diagnoses that have confused the evaluation in this group include "vascular" headache, cerebrovascular accidents, epilepsy, chronic nervous fatigue, menopausal tension, angioneurotic edema, urticaria, coronary artery disease, agitated depression and alcoholism. Among the 13 patients with proved pheochromocytoma the following conditions were either incidentally present or erroneously diagnosed before the true nature of the condition was established: anxiety attacks, epilepsy, cerebrovascular accidents, thyrotoxicosis, cyclothymic psychosis and hypoglycemic attacks.

THE RELATIVE UNRELIABILITY OF PHARMACOLOGIC TESTS, EITHER POSITIVE OR NEGATIVE, AS DIAGNOSTIC AIDS

In those cases of proved pheochromocytoma (table 2), four had Regitine tests, two of which were clearly positive (figure 1). One showed a sig-

nificant decrease of 26 mm. in the diastolic but a decrease of only 20 mm. in the systolic pressure. The fourth had a negative test, with a maximal drop of only 10 mm. in each reading.

Gifford et al.[6] reported no false-negative tests using intravenous Regitine on four patients with sustained hypertension of 150/110 mm. of Hg or greater due to pheochromocytoma. They noted four false-positives, however, in 107 patients without pheochromocytomas due to sedation.

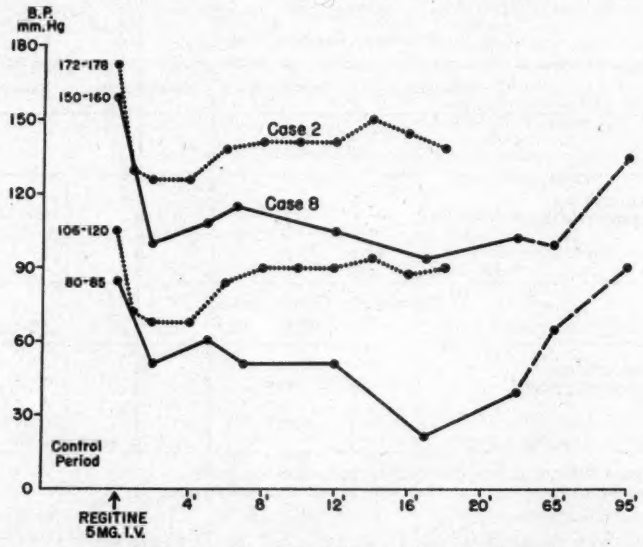

FIG. 1. Example of positive Regitine tests in two cases of proved pheochromocytoma, using criteria of $\frac{-35}{-25}$.

Both patients with false-negative tests in our series had borderline hypertensive basal resting blood pressure, 160/106 and 160/100 mm. of Hg, respectively. This was also true of the two patients with positive tests (figure 1).

The over-all results in our 79 cases and Gifford's 114 cases in which Regitine was given intravenously are compared in table 2. Our finding of two false-negative tests is unfortunate, since a "screening" test may be acceptable despite a large number of false-positives, but it fails in its prime function if false-negatives are common. Clearly, both series are much too small to give any reliable idea of the true incidence of either false-positive or false-negative tests, but we can simply observe that both exist.

Table 3 summarizes the results of all of the pharmacologic tests done in 10 of the 13 patients with pheochromocytomas. The Regitine test was positive in two out of four, Mecholyl in four out of seven, dibenamine in one

out of one, histamine in five out of six, and Etamon in one out of two. A sixth test, using Anectine (succinylcholine chloride) intravenously, is listed. We have not employed this intentionally as a diagnostic test, but obtained a striking hypertensive attack when it was used as a muscle relaxant in preanesthetic preparation in one patient with proved pheochromocytoma. Further investigation may indicate its usefulness along with the previously employed tests.

TABLE 3

Results of Six Diagnostic Pharmacologic Tests in 10 Patients with Proved Pheochromocytoma

Case	Regitine	Mecholyl	Dibenamine	Histamine*	Etamon with Sedation	Anectine
2	+	+				+
3			+			
4	0	0		++		
5		+		+		
7		±		±	0	
8	+					
10		0		+		
11		0+++		0	+	
12	0	00				
13				+		
Ratio of + Tests	2 of 4	4 of 7	1 of 1	5 of 6	1 of 2	1 of 1

* It has been our experience that histamine gives far more false-positive tests than Mecholyl.[5]

SUMMARY

Thirteen patients with proved pheochromocytoma, four of whom had Regitine tests, and 75 consecutive patients with hypertension but without pheochromocytoma, all of whom had Regitine studies, were reviewed.

This study has revealed to us the diagnostic importance of a syndrome of sustained or paroxysmal hypertension associated with diabetes mellitus, or a hypermetabolic state, or both. It is suggested, therefore, that pharmacologic tests should always be included in a routine examination of all hypermetabolic or diabetic patients with hypertension.

Thirteen cases of proved pheochromocytoma constitute too small a series to prove statistically the reliability of either the blocking or the provocative pharmacologic tests for the diagnosis of pheochromocytoma. It is suggested, however, that too many Mecholyl tests may be falsely negative, and too many histamine tests falsely positive. In our series one histamine test was falsely negative. We had no falsely positive Mecholyl tests. The Regitine test is reliable as a positive test, provided the patient has not been on Rauwolfia or phenobarbital, but is not utterly reliable as a negative test.

The urine catechol test is not to be considered pathognomonic for pheochromocytoma, since a high titer is found in many cases of anxiety with fluctuating high blood pressure.

Of 10 hypertensive patients treated with Rauwolfia, three had positive and six had suggestively positive Regitine tests, leading to five unnecessary pneumograms and three negative exploratory operations. There was one death following operation, due to lower nephron nephrosis attributed to the opaque dye used for aortography.

It is emphasized again that sedation with Rauwolfia or phenobarbital often produces falsely positive Regitine tests.

Summario in Interlingua

Nulle conclusiones pote esser formulate con respecto al relative fidelitate de varie pharmaco-essayos diagnostic usate pro identificar pheochromocytoma. Nostre studio pare indicar que un numero excessive de tests a Mecholyl es pseudo-negative e que un numero excessive de tests a histamina es pseudo-positive.

Es presentate un revista de 13 patientes con demonstrate pheochromocytoma e 75 patientes consecutive sin pheochromocytoma sed omnes subjicite a studios a Regitina. Le test a Regitina es fidel como test positive, providite que le patiente ha recipite nulle rauwolfia o phenobarbital, sed illo non es completemente fidel como test negative.

In un gruppo de 10 patientes sub tractamento a rauwolfia, tres habeva positive e sex habeva presumptivemente positive tests a Regitina, con le resultato de cinque non-necessari pneumogrammas e tres negative explorationes chirurgic. In un caso le operation esseva sequite per le morte del patiente.

Es signalate de novo que sedation con phenobarbital resulta etiam in pseudo-positivitate de tests a Regitina.

Le tetrade clinic de hypertension, attaccos paroxysmal, diabete mellite, e stato hypermetabolic es describite. Es proponite que studios pharmacologic es includite in le examine routinari de patientes con hypermetabolismo e hypertension con diabete.

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THE DIABETIC COMA OF ACUTE PANCREATITIS *

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INTRODUCTION

SEVEN cases of diabetic coma associated with acute pancreatitis have been observed at the Duval Medical Center during the last year. As the body of knowledge about this disease state has grown, we feel that there are certain specific characteristics by which it can be recognized.

Root [1] in 1937 described four cases. Schumaker [2] analyzed the literature and reported 25 cases in which diabetic coma occurred during an acute stage of pancreatic inflammation. Other reports list 29 additional cases.[3, 4, 5, 20–26]

There are numerous references to diabetic states following pancreatic necrosis.[6, 7, 8, 9] We hope to demonstrate that the diabetic coma of acute pancreatitis is, in certain cases, an entity separate from that seen in extensive physical destruction of the pancreas, with resulting glandular insufficiency.

Two cases will be presented.

CASE REPORTS

Case 1. The first was a 17 year old Negro female admitted in severe diabetic coma. Full details concerning the development of coma could not be obtained. It was known that the patient had been ill for eight days with a general sense of malaise, persistent headache and, for two days, a marked dizziness. She had always been obese, and had a marked taste for carbohydrates. She had also ingested and excreted noticeably more fluid than those about her. Five months prior to admission she had delivered her first child, who weighed nine pounds three ounces. Urine sugar was negative at that time. A vulvovaginitis began after delivery and persisted until admission. There was no history of nausea, vomiting, diarrhea or abdominal pain.

Upon examination the pulse was 168; temperature, 96.6° F.; respiration, 40. The blood pressure was unobtainable. Skin and mucous membranes were extremely dry. The abdomen was soft and bowel sounds were absent. There was no reaction even to painful stimuli.

The initial blood sugar was 930 mg.% and the CO_2 combining power 8.1 mEq./L. (figure 1). Serum amylase was not determined. The remainder of the studies are listed in figure 2. The intake and output figures need amplification. The patient was delirious. She dislodged four separate venoclysis sets (cut downs), after which fluids were given subcutaneously. At the time of death an estimated 5 L. remained unabsorbed in the subcutaneous tissues. The output figures are exact. Vigorous treatment was begun with insulin, antibiotics, fluids and electrolytes. By the second day the laboratory values had returned close to normal. The shock had also responded to some degree, but the patient remained delirious and critically ill. Temperature

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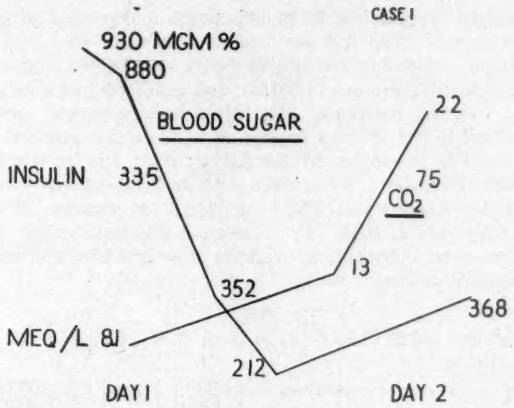

FIG. 1. Illustrating the blood sugar of 930 mg.% and CO_2 combining power of 8.1 mEq./L.

had climbed to 104° F. Severe vomiting began on the first hospital day and persisted until death occurred 52 hours after admission. The terminal episode was one of a three-hour period of shock.

Autopsy findings were:

1. Acute interstitial pancreatitis with focal areas of suppuration.
2. Fatty infiltration of the liver, moderately severe.
3. Atherosclerosis of aorta, grade I.
4. Vacuolization of proximal renal tubules.
5. Vulvovaginitis and cystitis.

There was no biliary tract disease, and the remainder of the organs were also normal.

Case 2. The next case was that of a 41 year old Negro male who had apparently been completely well until one month before admission, when polyphagia, polyuria,

WBC	19000		
DIFF	S87 L13		
HGB	14		
HCRIT	43		
Na			152
K			3.0
CO_2	8.1	13	22
Cl	104		116
INSULIN	335		75
INTAKE	8800		5800
OUTPUT	2300		4200
CASE I	DAY I		DAY 2

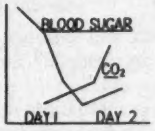

FIG. 2. Tabulation of laboratory findings in case 1.

polydipsia and weight loss totaling 40 pounds began and gradually increased from a mild to a severe degree. The day previous to admission he became oliguric, and abdominal pain with nausea but no vomiting occurred for the first time. The pain was of moderate intensity, without radiation, and localized just above the umbilicus.

This patient was also delirious. His initial history was so grossly inaccurate that he was admitted to the urology service as a diagnostic problem. Medical consultation a few hours later recognized the diabetic state, and he was promptly transferred to the medical service. When first examined the patient was a dehydrated, wasted man in coma. Pulse was 100 and regular; blood pressure, 90/60 mm. of Hg; respiration, 36; temperature, 101.6° F. Abnormal physical findings were limited to the vital signs, the severe dehydration, evidence of weight loss, and slight but definite spasm of the epigastric muscular wall.

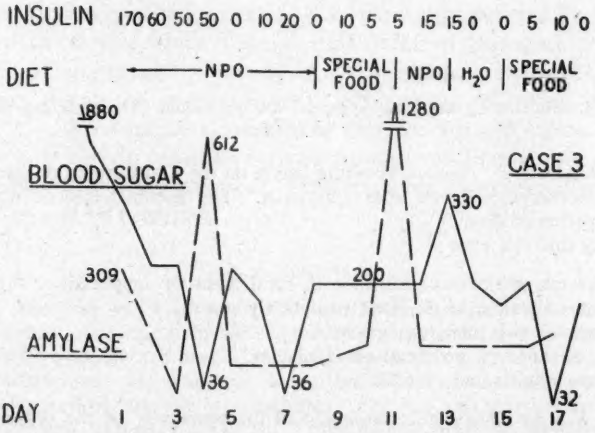

FIG. 3. The rapid fall in blood sugar level and the episodes of hypoglycemia following exacerbations of the pancreatitis are illustrated. The first feedings on the ninth day were followed by a rise in serum amylase and other evidence of acute pancreatitis. NPO = nil per os.

Laboratory data and diet are recorded in figure 3. The first blood sugar was 880 mg.%; serum amylase, 309 Somogyi units. In 12 hours the blood sugar dropped to 354 mg.%.

A number of exacerbations of the pancreatic inflammation occurred during the hospital course. The hyperglycemia of the initial attack and of the first two recurrences were each followed by a dangerously low blood sugar. The amount of insulin given in the preceding hours was not sufficient to account for this finding. This patient received only 10 units of regular insulin in the 24 hours preceding the seventh day, with the blood sugar falling from 220 to 36 mg.%. During the third such event the patient was given 200 gm. of glucose each day, but this did not prevent a brief episode of hypoglycemia.

In each case the low blood sugar followed an exacerbation of the pancreatitis.

Stimulation of the digestive function of the gland apparently caused these recurrences. Partial foods, such as egg albumin, Jello and glucose, were begun on the ninth day, with the amylase rising to 1,280 units early on the eleventh day. A similar episode occurred on the twenty-fourth day (figure 4), when the whole foods of a diabetic diet were ingested for the first time.

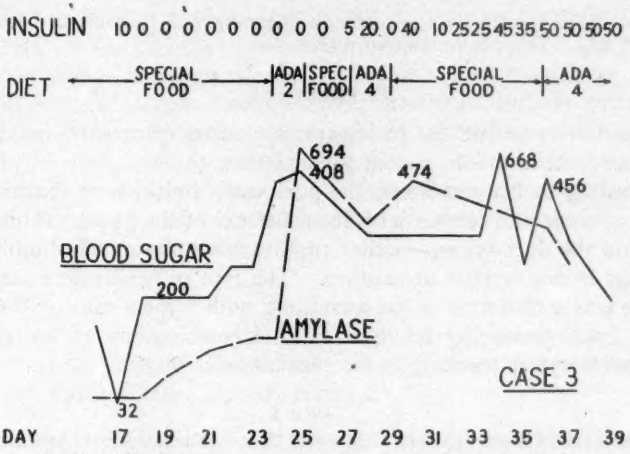

FIG. 4. The relationship of stimulation of the pancreas to exacerbation of pancreatitis is again illustrated following the twenty-fourth day.

Hydration was accomplished by the use of blood and plasma as well as fluids and electrolytes. The relative ease with which this was accomplished is reflected in the intake and output figures as well as in the nonprotein nitrogen values (figure 5). This is in direct contrast to another case of pancreatitis (table 1), in which hemodilution occurred but the water deficit could not be corrected by fluids and electrolytes alone. The patient under discussion was finally stabilized on a daily dose of

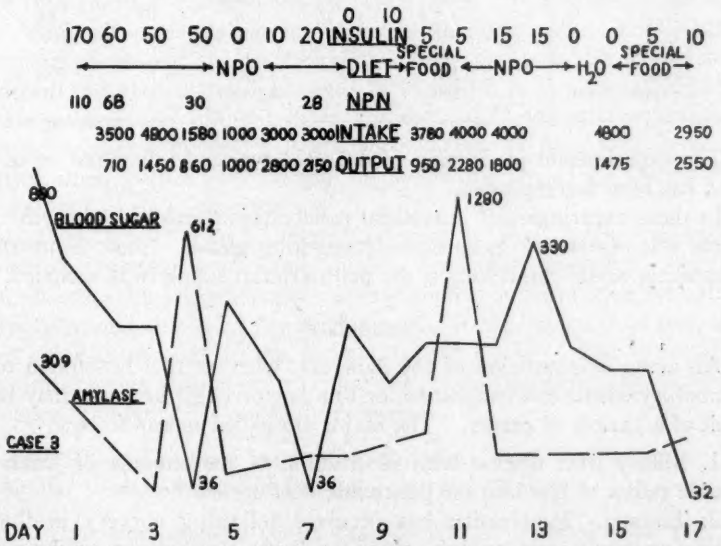

FIG. 5. Studies of the dehydration and its correction with plasma and whole blood in addition to water and electrolytes. NPO = nil per os.

55 units of NPH insulin. He is presently doing eight to 10 hours of heavy manual labor each day. There have been no recurrences.

Pathogenesis

When one considers the pathogenesis of acute pancreatic inflammation, other than from infection, certain principles are evident.

According to many writers, the pancreatic digestive or exocrine secretions must come into contact with the substance of the gland. This requires a defect in the duct system—either rupture from abnormally high pressure, or leakage in one manner or another. The type of pancreatitis may depend upon the major character of the secretions, with trypsin causing the necrotic variety, lipase producing fat necrosis, and combinations of inorganic materials and enzymes resulting in the edematous variety.[15]

Table 1

Combined Studies of a Separate, Unreported Case. (The inability to hydrate with fluids and electrolytes is illustrated in the intake and output figures. Hemodilution is evident in the hemoglobin values.)

Case 2	Day 1	Day 2	Day 3
WBC	17,750	26,000	
Differential	B7 S86 L7	B18 S74 L8	
Hemoglobin	16.5	7.5	9.5
Hematocrit		26	31
CSR		30	
A/G		3.8/2.9	
Na	131	133	131
K	6.2	4.0	3.1
CO_2	5.4	19	23
Cl	107	109	104
Insulin	120	45	105
Intake	2,200	3,890	2,000
Output	1,830	3,000	1,250

The experimental production of different types of inflammation of this gland has been accomplished.

In these experiments,[19] interstitial pancreatitis developed when the duct system was obstructed in an actively secreting gland. Acute hemorrhagic pancreatitis would result only if the main arterial supply was occluded.

Etiology

An acute inflammation of the pancreas, whether this be limited to inflammatory edema and congestion, or to a hemorrhagic necrosis, may be the result of a variety of causes. The major etiologies appear to be:

1. Biliary tract disease with obstruction of the ampulla of Vater and possible reflux of bile into the pancreatic duct system.[13, 14]

2. Trauma. Pancreatitis has occurred following surgery in the immediate anatomic vicinity of the gland.[15] It has also been caused by a penetrating peptic ulcer.

3. Infection by direct spread from a nearby focus, or borne by lymph or blood streams. The general viral disease mumps is included in this category.

4. Obstructions to pancreatic duct drainage, which may cause this disease under certain circumstances. The obstructions include occlusion of the ducts by detritus, by pancreatic calculi, by metaplasia of the duct epithelium, or by sludging of the pancreatic secretions. Other types may be due to edema of the duodenal mucosa, such as that following prolonged ingestion of alcohol, or a mechanical blockage caused by pressure from a duodenal diverticulum or tumor formation.

Characteristics

The characteristics of the diabetic coma of acute pancreatitis, which differs from uncomplicated diabetic coma, are:

1. The elevated blood sugar drops more rapidly than does that of uncomplicated coma. An example of this is a blood sugar of 880 falling to 354 mg.% in 12 hours after the administration of only 170 units of regular insulin.

2. The serum amylase is elevated. Routine amylase determinations have been done on all admissions of diabetic acidosis and coma for one year. We have not had a single abnormally high value in any case that did not have some positive finding of pancreatic inflammation associated with the diabetic state.

3. Dehydration is extreme in the severe cases. It is of no greater degree than in simple coma, but it has different characteristics. These patients cannot be adequately hydrated without plasma and/or whole blood, as well as fluids and electrolytes. In acute pancreatitis it is believed that both plasma volume and red cell mass are reduced.[11] Animal experiments[12] show a significant difference in the survival rate of dogs with acute pancreatitis when treated with albumin or dextran to correct the plasma deficit as measured in these experiments.

4. There appear to be brief periods during the acute stage of pancreatitis —both the initial attack and during exacerbations—when significant amounts of insulin are produced. This statement is based upon the episodes of hypoglycemia shown in the second case. It has occurred in five of the seven cases discovered at the Duval Medical Center. The alternate explanation for this phenomenon is that the production of the hyperglycemic substance, glucagon,[10] is suddenly reduced.

Other differences from uncomplicated diabetic coma present in our series are similar to those described by Root[1] and amplified here.

5. Prostration is more severe than would be expected with a systolic blood pressure of more than 100 mm. Hg.

6. There is a failure to improve despite adequate therapy. Delirium is particularly marked, sometimes with hallucinations.

7. Abdominal examination may reveal tenderness and spasm in the epigastrium. If the patient is unconscious when seen for the first time, guarding and spasm may still be elicited. Bowel sounds are absent. In the present series, either vomiting or diarrhea, or both, have occurred during the unconscious period.

8. Dr. Root listed sweating as a characteristic common to associated coma and pancreatitis. This series of cases all had the dry skin usually seen in uncomplicated coma.

9. Abdominal pain with those characteristics of pancreatic distribution is usually present. It may be much less severe than in an uncomplicated pancreatitis. After the onset of the pain, coma may develop relatively rapidly. Also, if symptoms of unrecognized diabetes mellitus precede the pain, coma develops rapidly.

The remainder of the studies performed do not distinguish uncomplicated diabetic coma from the condition under discussion. The degree of hyperglycemia is in no way characteristic of this disease. It has ranged from 432 to 930 mg.%. The white blood cell count may be normal or elevated in either condition. The initial episode of shock is identical to that seen in many cases of severe coma. The pulse is quite labile, varying from 60 to 168 in this series, and has no distinguishing features. The lipemia, which is partially due to an elevated cholesterol, is not diagnostic. Calcium values have been normal, and no evidence of excessive muscle irritability was discovered.

The febrile course in all of our seven cases cannot be relied upon to diagnose pancreatitis, as this is frequently present in uncomplicated diabetic coma.

Discussion

There are certain features of these cases which we believe to be accurate:

All had acute pancreatitis and were in diabetic coma.

Four of the seven patients have died. Each of these cases exhibited acute changes in the pancreas. Two of the four also had the widespread fibrosis of chronic pancreatic inflammation, and each had had numerous episodes of acidosis and coma. One of the three surviving cases has a chronic recurrent pancreatitis; in this case, diabetic symptoms preceded those of pancreatitis. The remaining two cases of this series had no history of previous attacks of pancreatic inflammation and have had no recurrences. In each of these, the symptoms of diabetes mellitus preceded anything which could be considered even suggestive of pancreatitis. Their disease was that of acute interstitial pancreatitis, which is known to heal with little else than fibrous tissue about the acinar structures to prove such an event occurred.[14]

If we return to those principles by which experimental pancreatitis may be produced, namely, stimulation of the gland with some leakage of the secretions into the parenchyma, there is a suggestion that this is the sequence of events which occurs in this state.

An elevated blood sugar can be a stimulus to the production of digestive secretions.[16, 17] In severe diabetic acidosis the high blood sugar is accompanied by dehydration which may be presumed to cause some sludging of the pancreatic secretions. Under these circumstances a back pressure leakage from the duct system may result in acute pancreatitis.

Another factor may be preceding defects in the pancreatic duct system predisposing to leakage and due to pancreatic fibrosis. Studies of the pathologic changes in the pancreas of diabetics report the over-all incidence of fibrosis to be as high as 83%.[18] It has been present in 84% of 13 consecutive, unselected diabetics dying of a variety of causes at our hospital during the last year. This lesion, most commonly interacinar, is more frequent in the diabetic than in the nondiabetic pancreas.

If these data be accurate, then the "diabetic coma of acute pancreatitis" is, in some cases, the "acute pancreatitis of diabetic coma."

Summary and Conclusions

Two cases of diabetic coma associated with acute pancreatitis have been reported.

The distinguishing characteristics of this associated state seen in a series of seven cases are:

1. Rapid fall in blood sugar levels.
2. Elevated serum amylase.
3. Water-resistant dehydration which responds to expansion of the blood volume.
4. Brief periods of increased insulin production or reduction of glucagon.
5. Severe degree of prostration.
6. Failure to improve despite therapy.
7. Abdominal pain of pancreatic distribution.
8. Abdominal tenderness or spasm.
9. Sweating at some stage of the disease.

Certain data suggest that the acute edematous pancreatitis is the result rather than the cause of the diabetic coma.

Summario in Interlingua

Es presentate duo casos de coma diabetic associate con acute pancreatitis. Le characteristicas clinic e laboratorial que differentia coma diabetic con pancreatitis acute ab coma diabetic sin complication es le sequente:

1. Le elevate nivello de sucro del sanguine descende plus rapidemente in le stato combinate.

2. Le amylase del sero es elevate.

3. Le grado de dishydratation es extreme, e rehydratation non es effectuabile sin le uso de plasma e/o sanguine integre in ultra de aqua e electrolytos.

4. Fluctuationes del nivellos de sucro del sanguine occurre con rapiditate, e un acute exacerbation del pancreatitis es a vices sequite per un sever hypoglycemia.

5. Le prostration excede le grado de severitate a expectar in le presentia de un pression systolic de plus que 100 mm Hg.

6. Melioration non occurre in despecto de therapia adequate.

7. Sensibilitate e spasmo muscular pote esser presente in le epigastrio. Vomito e diarrhea occurre frequentemente durante le periodo de inconscientia.

8. In certe casos transspiration occurre.

9. Dolor abdominal con le characteristicas del distribution pancreatic es usualmente presente.

Le sequente factores non differentia complicate ab non-complicate coma diabetic: Grado de hyperglycemia, numeration leucocytic, presentia de choc, rapiditate del pulso, e nivellos seral de cholesterol o calcium.

Le analyse del historia e del curso hospitalari de un total de septe casos de coma diabetic con acute pancreatitis pare indicar que in certe casos le stato diabetic precede le declaration de pancreatitis acute. Es discutite un mechanismo per que acidosis diabetic precipita possibilemente acute pancreatitis.

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AN EVALUATION OF DIETARY PROTEIN IN THE TREATMENT OF LIVER DISEASE*

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IN 1937 the diet prescribed for patients with cirrhosis was kept low in protein to avoid burdening the sick liver.[1] Ten years later [2] a diet of approximately 140 gm. of protein was generally accepted, and tube feeding was prescribed for those who were comatose or otherwise could not take this amount voluntarily. After another 10 years it is stated in the most recently published textbook of medicine [3] that the diet "should at least be adequate in all nutrients necessary for a normal individual," and complete withdrawal of protein is advised for the patient entering into hepatic coma. Thus the pendulum has swung almost all the way back to where it was 20 years ago.

The story of the recent changes in the popularity of dietary protein has four chapters: (1) the initial enthusiasm for a high protein diet; (2) the realization that patients may improve rapidly on a low or normal protein diet; (3) the rediscovery of the potential toxicity of protein; and (4) the present indications for excess, normal or reduced dietary protein. It is necessary that Chapter 4 be preceded by the first three so that some insight may be gained into what makes the pendulum of protein popularity swing back and forth. An evaluation of the papers and data responsible for the frequent changes in authoritative opinion may allow a straighter course to be charted in the future determination of other symptomatic therapies.

I. THE INITIAL ENTHUSIASM FOR A HIGH PROTEIN DIET

Patek [4] first reported in 1937 his observations that patients improved more rapidly when forced to eat a well rounded, nutritious diet. At that time the rationale was based on the occurrence of multiple nutritional deficiencies in most patients with cirrhosis. Within a few years of the publication of Patek's first report a large number of investigators described the effectiveness of protein or its constituents in protecting the animal liver against toxic agents [5, 6] or specific dietary deficiencies.[7, 8] In 1948 Patek et al.[9] summarized the results obtained in the treatment of 124 patients with a diet containing 140 gm. of protein, 365 gm. of carbohydrate and 175 gm. of fat, supplemented by yeast or other vitamin preparations. When these patients were compared with a control series of patients admitted to other hospitals during the period from 1920 to 1940,[10] the effectiveness of the

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nutritious diet in relieving ascites and returning a significant number of patients to a state of relative health was striking.

Since Patek's original observations innumerable clinical papers have confirmed the effectiveness of a high protein diet in cirrhosis, and the amount of protein prescribed has occasionally risen to levels of 200 to 300 gm. per day,[11] or to 2 to 2.5 gm. per kilogram of body weight.[12] Following studies conducted during World War II,[13, 14] an intake of around 200 gm. of protein has also been urged in the treatment of acute infectious hepatitis.[15]

The effectiveness of a high protein diet referred to above was not established by studies controlled according to the best concepts of randomization of patients and limitation of variables other than those under investigation. Nevertheless, it is impossible to conclude that the diet may not have been one of the factors responsible for what is undoubtedly a better prognosis than was given to patients with cirrhosis 20 years ago.

II. Effectiveness of Lesser Amounts of Protein

In undertaking a study of the effectiveness of a high protein diet, Klatzkin noted that patients improved rapidly during a control period of bed-rest, abstinence from alcohol, and a limited dietary intake of only 1 gm. of protein per kilogram of body weight.[16] His patients improved as rapidly as those fed a high protein diet by Volwiler,[17] except for a slightly more rapid rise in serum proteins and disappearance of fat from the liver cells in the latter group.

At the same time Eckhardt,[18] during studies of the effects of intravenous amino acids as the sole source of dietary protein, noted that one patient improved rapidly while in negative nitrogen balance. This single observation was followed by a study [19] in which three acutely ill patients improved clinically on a diet calorically adequate but devoid of protein. In contrast, no improvement was noted in a later study [20] in which only glucose and vitamins were given for the first 10 days in the hospital. In both studies the liver morphology improved only after protein was added to the diet. In three patients with infectious hepatitis Plough [21] demonstrated significant improvement while the patients continued in negative nitrogen balance.

The above studies demonstrate that, although a minimal intake of protein is probably necessary, a high intake is not essential for improvement to take place in either cirrhosis or hepatitis. Other factors inherent in hospital care must play a part, and only a properly controlled therapeutic trial can determine whether a high protein intake is more effective than a normal diet in improving hepatic function in the cirrhotic. Because the prolonged course of each patient allows the introduction of innumerable variables, such a study would be difficult but not impossible to perform. The difficulty is no excuse for the elimination of simultaneously treated controls in future studies.

III. The Rediscovery of Protein Toxicity

In 1952 Gabuzda [22] reported that patients with cirrhosis given ammonium containing cation-exchange resins developed a neurologic syndrome indistinguishable clinically and by electro-encephalogram from spontaneous impending hepatic coma. Following production of the same syndrome by the oral administration of ammonium salts, urea and increments of dietary protein,[23-25] it was concluded that nitrogenous substances of all kinds might be contraindicated in severe liver disease because of their deleterious effects on the central nervous system. Chronic protein toxicity has now become a well recognized syndrome in patients with severe liver disease and varying degrees of portacaval collateral circulation,[26] and it is now recognized that all dietary protein should be omitted as soon as coma appears imminent.[27, 28]

When those who recently documented the severe cirrhotic's intolerance of protein and other nitrogenous substances [22-26] reviewed the literature, they found that the syndrome of "meat intoxication" in dogs with Eck's fistulas was first described in 1893,[29] just 16 years after the first Eck's fistulas were performed. In 1895 Eck's fistulas were shown to result in an elevation of blood ammonia.[30] During the 20th century these observations have been repeated at sporadic intervals, and they may have been partly responsible for the avoidance of excessive protein in the diet of cirrhotics prior to 1937. It is still not clear how much of the symptom-complex accompanying increased protein intake in certain susceptible patients is due to ammonia poisoning and how much to other noxious nitrogenous substances, or what relative parts impaired hepatocellular function and portacaval shunting of blood play. From the standpoint of this discussion, the important thing to emphasize is that there is no evidence, either in man or in the experimental animal, that excess dietary protein harms the liver. "Protein toxicity" is a disorder of the brain, not the liver.

IV. Present Indications for a High or Low Protein Diet

Before a decision can be made as to whether a patient with acute or chronic liver disease should be forced to eat a high protein diet, the evidence must be further reviewed to seek an answer to the following three questions.

1. Are there any acceptable data suggesting that excess dietary protein may hasten the healing of the damaged liver?
2. Do malnourished patients with cirrhosis return more rapidly to a state of normal nutrition on a forced dietary intake?
3. If there is much chance that either of the above is true, how common, diagnosable and reversible is protein toxicity?

1. Unfortunately, there are no animal studies directly applicable to the first question. Only a small number are concerned with the treatment of already established liver disease, and in all of those either one dietary supple-

ment is compared with another, or a high protein diet is compared with supplements, but not with a normal protein diet.[31]

A recent study by Brandt et al.[32] has some bearing on the problem in an indirect way. It was found that in both normals and cirrhotics a protein but not a carbohydrate meal resulted in an increase in splanchnic blood flow and oxygen consumption. On the questionably valid assumption that a diseased organ should be rested, the authors conclude that patients should be fed just enough protein to maintain them in positive nitrogen balance. One could take the opposite point of view—that the increased blood flow following a protein meal might benefit the hepatic cells. A rise in portal vein pressure observed by the same authors may be a more valid contraindication to a large protein meal, at least in patients with esophageal varices.

In the last five years two large-scale controlled comparisons of high and normal protein intakes in viral hepatitis have been performed, with opposite conclusions. Among prisoner volunteers inoculated with homologous serum jaundice a high protein, low fat diet resulted in a slightly longer illness and more complications than did normal prison fare.[33] Among American troops who contracted infectious hepatitis in Korea and Japan,[34] forced consumption of a high protein, high calorie, supplemented diet significantly shortened the duration of illness when compared with a normal diet consumed ad lib. In a second study it was determined that the effective element of the diet was the protein content rather than the calories or supplements. Retrospective analyses revealed that the high protein diets shortened the mean duration of illness by preventing a further rise in serum bilirubin after hospital admission in a significant number of patients. The highest protein diet, however, resulted in a slightly increased incidence of residual abnormalities of questionable significance. The explanation for the different results of the prisoner and Army studies is not apparent, but it seems probable that cautious forcing of a high protein, high calorie diet early in infectious hepatitis will shorten the duration of jaundice by about 20%. It is impossible to state whether these results in viral hepatitis are applicable to patients with cirrhosis.

2. The great majority of patients with Laennec's cirrhosis are depleted in body protein stores. In some measure this is a reflection of the poor diet consumed while the cirrhosis was developing, but in most the protein depletion results from many months of illness and anorexia. In the few patients with alcoholic cirrhosis who remain off alcohol, recovery is associated with a striking return of flesh that is probably both lean body mass and subcutaneous fat.

Can this return to normal nutrition, i.e., good health, be hastened by forcing food? Again, competent therapeutic trials are lacking, but the nitrogen balance technic has allowed the gathering of a great deal of applicable data. Forsyth[35] has shown that in soldiers malnourished because of extensive war wounds, nitrogen retention is proportional to nitrogen intake,

provided the calories are adequate. There is no tapering of the effect. The more protein ingested, the more positive is the nitrogen balance, and presumably the more rapid is the repletion of the patient.

For these concepts to apply to the patient with cirrhosis, one must assume that the over-all handling of dietary protein in this disease is relatively normal. Gabuzda and Davidson [36] present data very similar to that gathered in normals by Forsyth,[35] but demonstrate in two patients an increase in the fraction of dietary nitrogen retained as liver function improves. Plough et al.[21] concluded that, at least as demonstrated by the nitrogen balance technic, the handling of dietary protein by patients with liver disease was not significantly different from normal. More recently, Plough et al.[37] have demonstrated that in cirrhotics, as in normals,[38] supplementary calories increase nitrogen retention by from 1 to 6 mg. of nitrogen per calorie added above the basal requirement. In Plough's study the amount of nitrogen spared per added calorie was directly related to the level of protein in the diet.

Thus it may be assumed that, since dietary protein and calorie increments place patients in more positive nitrogen balance, prolonged increased intake should hasten a return to a normal state of nutrition. The amount of nitrogen lost because the liver may not be completely efficient would not seem to be clinically significant. A few calculations will illustrate the potential usefulness of this concept. Assume that 1 gm. of nitrogen is contained in 32 gm. of lean body tissue or approximately 100 gm. of fatty tissue (including extracellular fluid).[39, 40] A cirrhotic who has lost 25 Kg. of body weight (discounting ascites or edema) might theoretically have to gain back roughly 10 Kg. of lean body mass and 15 Kg. of fatty tissue or 465 gm. of nitrogen. If he were in positive nitrogen balance by only 1 gm. of nitrogen per day it would take him at least 465 days to reach normal nutrition. If he could be made to retain at least 3 gm. per day, the time might be cut to about six months. Since for these estimations it is assumed that the patient is in positive balance every day of the year (which is probably not the case), the potential durations are undoubtedly longer than 18 or six months, as the case may be. In actual practice, it takes from one to two years for the severely depleted cirrhotic to return to a normal state of nutrition.

3. It would seem, therefore, that it is worth while to encourage the patient with cirrhosis or hepatitis to eat a high protein, high calorie diet, provided protein toxicity can be diagnosed early and treated effectively, as seems to be the case.[27, 28] Early clinical signs to look for are minimal confusion, untidiness, a far-away look in the eye, a coarse or flapping tremor that is accentuated by placing the limb under tension, and steadily increasing daytime drowsiness with a tendency to wander at night.

In the laboratory the electro-encephalogram and the blood "ammonia" may be helpful when they can be obtained. The former is extremely sen-

sitive and relatively specific.[41, 42] It is probably the most useful "liver function test" introduced in recent years. The characteristic abnormalities of protein toxicity are illustrated in figure 1. The blood "ammonia" determination is a technically and biologically erratic test, and obviously does not reflect the deleterious effects of the dietary protein upon the brain.

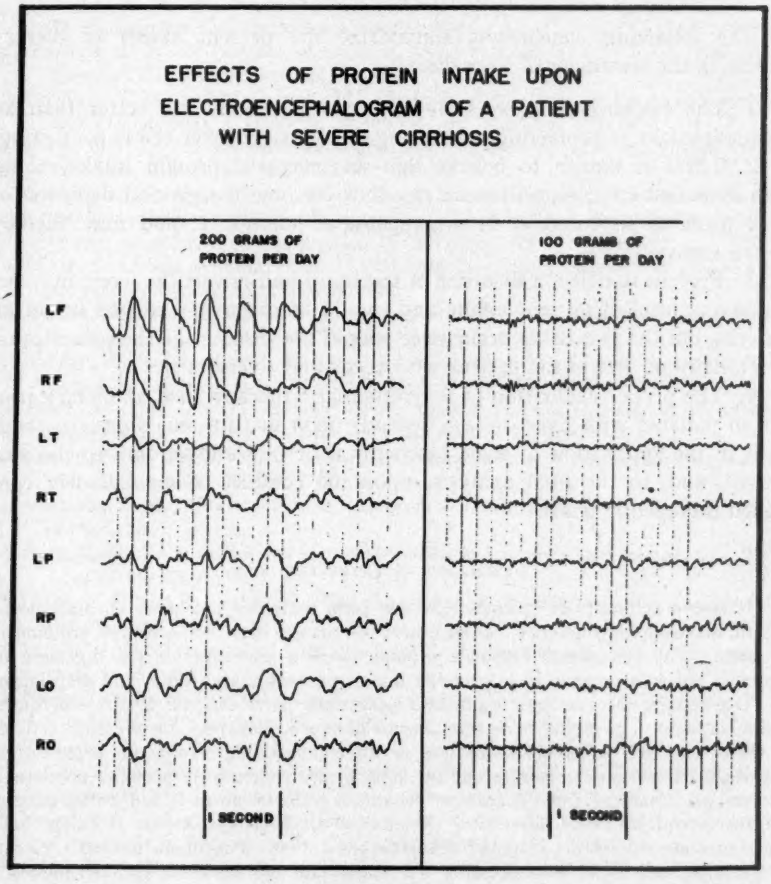

FIG. 1.

The reversibility of the syndrome of protein toxicity has been demonstrated many times. At its onset, dietary protein should be withdrawn completely for one or two days and then increased slowly by about 25 gm. increments until a safe but adequate or therapeutic level has been obtained. Some patients are extremely sensitive to dietary protein, and in this situation the physician must be satisfied with keeping his patient on a deficient protein

intake indefinitely. It is possible that an oral antibiotic such as Neomycin,[43] or supplements of glutamic acid[44] or arginine,[45] might enable the patient to consume his minimal protein requirements, but these measures have not yet been sufficiently tried.

Conclusions

The following conclusions summarize the present status of dietary protein in the treatment of liver disease:

1. The evidence that excessive amounts of protein are better than an adequate intake in protecting or treating the damaged liver cell is conflicting.
2. There is reason to believe that an increased protein intake, along with abundant calories, will more rapidly overcome the general depletion of body proteins so common in decompensated cirrhotics, and may thereby hasten recovery.
3. Protein toxicity, a disorder of the brain and not of the liver, may occur at any level of protein intake and should be carefully watched for in all patients, but the fear of its occurrence should not discourage the prescription of a nutritious diet in the patient who needs and tolerates it.
4. The proper evaluation of a symptomatic therapy such as dietary protein in patients with liver disease depends upon mature and objective judgment in the application of basic biochemical or physiologic data to the sick patient, and, in the final analysis, upon the conduct of meticulously controlled therapeutic trials.

Summario in Interlingua

Il esseva demonstrate recentemente que certe patientes con sever chronic morbo hepatic disveloppa symptomas mental e nervose quando illes recipe troppo proteina in lor dieta. Iste symptomas responde promptemente a un reduction del ingestion de proteina, sed si le excesso in le proteina dietari es continuate, coma pote disveloppar se. Iste recente observationes significa le necessitate de re-evalutar le placia de dietas a alte contento de proteina in le tractamento de morbo hepatic. Le presente articulo es un revista del pertinente datos que es nunc disponibile. In acute hepatitis infectiose il ha essite demonstrate que un dieta a alte contento de proteina accelera le retorno del tests del functionamento hepatic a valores normal, sed certe adverse effectos lateral ha essite describite. Relative a cirrhosis del hepate il existe nulle ben controlate studios del responsa del patientes a dietas a contento normal e elevate de proteina, sed il es le impression del majoritate del medicos que cirrhoticos a depletion nutritional se meliora plus rapidemente quando tractate con dietas a alte contento de proteina. Del altere latere, le complete abstention de proteina durante periodos de inter duo e tres dies e le administration de un antibiotico como per exemplo neomycina ha recentemente essite recognoscite como multo efficace in le tractamento de coma hepatic. Il existe nulle prova que le proteina causa injurias in le cellulas hepatic, sed il ha satis forte indicationes que patientes a depletion dietari —con o sin cirrhosis—retine plus alte proportiones de nitrogeno quando illes ingere grande quantitates de nutrimento, specialmente proteina. Le electroencephalogramma ha devenite un medio de grande utilitate in le detection de toxicitate proteinic al initio

de su disveloppamento. Le conclusion es formulate que dietas a alte contento de proteina continua haber su placia in le tractamento de acute e chronic morbo hepatic e es completemente salve, providite que le signos e symptomas de toxicitate es rememorate.

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THE USE OF A FORMULA DIET FOR WEIGHT REDUCTION OF OBESE OUT-PATIENTS *

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TOTAL replacement of natural food by a nutrient mixture was used for weight reduction of obese patients almost a century ago. In 1866 Karell [1] described a liquid diet providing only three or four glasses of creamy milk per day, taken at carefully observed intervals. In 1908 Moritz [2] reported treatment of nine obese patients with whole milk or buttermilk given as the sole nutriment for periods of up to 61 days. Harrop [3] in 1934 recommended the use for two-week periods of a skimmed-milk-and-banana diet alternated with a conventional, calorically-restricted mixed-food diet. The majority of patients in each of these studies accepted the dietary restriction and lost weight in a satisfactory fashion. However, none of the diets was tested on a large enough group of patients or for a long enough time to define its practical value, and this method of treatment never found general application.

More recently, liquid formula diets have been used in a variety of metabolic studies.[4-7] The successful long-term use of formulas in these studies and for weight reduction of patients in the hospital suggested that a similar mixture might be useful for treatment of obese out-patients. Whether such a rigid diet could be maintained outside the hospital under the temptations and pressures of normal social activity was uncertain. The current study was undertaken to answer this question.

METHODS

The group of 106 obese patients—11 men and 95 women—ranged in age from 14 to 67 years. The initial weights varied from 147 pounds (66.6 kg.) to 380 pounds (172.9 kg.), and averaged 224 pounds (101.6 kg.). Most of the patients came to the hospital knowing only that it had an obesity clinic, and were unaware of the type of diet they were to receive. A few had heard about the formula diet and had come to the clinic ready to try it.

In the early stages of the work a brief training period in the hospital was considered necessary for the patient's introduction to the diet. Accordingly, each of the first 49 patients was admitted to the hospital for four days, during which he had a general medical examination, was started on formula diet, and was instructed in its preparation and use. The subsequent 57 patients were treated entirely in the out-patient clinic.

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An explanatory lecture was given to all patients. In the hospital, this was done with groups of four; in the clinic, the lecture was given either individually or to groups of various sizes, the largest of which contained 28 patients. The discussion dealt with the origin of the formula diet, the rationale for its ingredients, theories of weight reduction, technics of dieting, and the practical advantages and disadvantages of formula therapy. Specific problems likely to arise in using the formula at home were anticipated as far as possible. Patients were told not to use any drug adjuncts (thyroid, Dexedrine, etc.). After the discussion, a dietitian supervised each patient in the preparation of one day's supply of formula.

TABLE 1

Composition and Preparation of One Daily Unit of Formula Mixture

Ingredient	Quantity	Approx. Weight (gm.)	Protein (gm.)	Fat (gm.)	Carbohydrate (gm.)	Calories	Sodium (mg.)
Dextrose	6 level tablespoons	54	—	—	54	216	—
Corn oil*	2 level tablespoons	27	—	27	—	243	—
Evaporated milk*	10 ounces	316	22	25	31	437	316
Water	8 ounces	—	—	—	—	—	—
Total			22	52	85		316
Total calories			88	468	340	896	
Per cent of calories			10	52	38		

Equipment: 1 standard measuring tablespoon.
1 standard measuring 8-ounce cup.
Hand egg beater and mixing bowl or electric mixer or blendor.

* Mazola Corn Oil and Borden's Evaporated Milk were used in the present study.

The patients returned to the clinic at weekly or bi-weekly intervals and were seen individually each time by the same physician. At each visit the patient's weight was plotted on a graph, physical examination and laboratory tests were performed when indicated, and any dietary difficulties were discussed. The time spent varied from five to 30 minutes, with an average of about 12 minutes per patient. Although no organized group meetings were held after the initial discussion, the patients saw each other regularly in the waiting room of the clinic. They became acquainted and discussed mutual problems.

Preparation and Instructions for Use of the Formula Diet: For home use, a formula mixture described previously [7] was converted into household measures and the total amount was adjusted to a unit of approximately 900 calories (table 1). The ingredients were chosen because of availability at the time of the study. Presumably other kinds of vegetable oil and other brands of evaporated milk would have been equally satisfactory. The mixture was inexpensive: a week's supply of the milk, oil and dextrose could be purchased in the New York City area for about $1.85. In addition, a daily

multivitamin preparation was prescribed, since the unsupplemented formula mixture was deficient in ascorbic acid and a number of the B vitamins. Although the formula diet was also low in iron, previous studies [7] of hospitalized obese male and female patients had shown that a supplement could be omitted for periods of at least six to eight months without development of anemia. Since the duration of treatment of out-patients with formula diet only was to be shorter than the periods in the hospital, it was decided to avoid possible gastrointestinal irritation by iron supplements.

The patients were directed to prepare a fresh unit of formula each day, and to divide it into five or six feedings to be taken at two- to three-hour intervals. The exact schedule and allotment of intake were left to individual preference. The mixture was to be blended thoroughly during preparation and shaken well before each aliquot was poured. (When homogenization had not been complete, a thin layer of fat floated to the top during storage, but could be easily redistributed by shaking.) The additional intake of water, black coffee and tea, noncaloric sweeteners, unflavored carbonated water and low-calorie soda beverages was unrestricted. Bouillon soups or hot water with lemon was occasionally permitted. A daily fluid intake of 1,500 to 2,000 ml. was suggested to avoid excessive urinary concentration.

Almost all patients found the formula palatable in its original form or with such minor variations as vigorous shaking to produce a frothy consistency, mixing individual feedings with ice chips or pouring them over ice cubes, addition of small quantities of chocolate or other flavoring, and dilution with water, carbonated water or coffee. Patients who had to eat away from home carried the formula in thermos bottles. Despite various problems presented by work, school or social schedules, many patients adjusted well to their situations.

Results

Adherence to the Diet: There were three patterns of adherence to the diet: (1) some patients were completely scrupulous; (2) others used the formula as a basic dietary staple with the regular addition of natural food in amounts small enough to permit continuing weight loss, and (3) the remainder either abandoned the diet or took so much excess food that progress was lost.

Table 2 indicates the distribution of patients with respect to the first week in which they reported food supplementation and the number of weeks during which they continued losing weight. Most of the patients seemed ready to admit any deviation from the strict formula schedule. If, however, a patient's report was in doubt, he was listed as having taken food within the first two weeks. The table shows that 23 of 106 patients stopped the diet completely within the first two weeks, and an additional 14 dropped out in the next two weeks—a total of 35%. Of 59 patients who took supplemental food in the first two weeks, 28 continued to lose weight for more than five

TABLE 2

Duration of Adherence to Formula Diet Regimen

The table shows the week in which food supplementation first occurred and simultaneously compares the length of time in which each patient was able to continue losing weight. (The figures refer to the number of patients in each category. The percentages refer these numbers to the total group of 106 patients.)

Week of First Episode of Food Supplementation	Weeks of Continuous Weight Reduction					Total
	0–2	3–4	5–10	11–20	Over 21	
0–2	23	8	11	10	7	59 (56%)
3–4		6	6	3	3	18 (17%)
5–10			7	3	3	13 (12%)
11–20				7	2	9 (9%)
Over 21					7	7 (7%)
Total	23 (22%)	14 (13%)	24 (23%)	23 (22%)	22 (21%)	106

weeks, and 17 for more than 11 weeks. Thus, almost half of the patients who departed from the strict formula regimen nevertheless continued to lose weight, although at a slower rate than those who followed the diet more rigorously. Of the 16 patients in the most scrupulous group, seven patients followed the diet strictly for over 21 weeks, and nine others did so for periods of 11 to 20 weeks, giving a total of 16% in this class. As a measure of over-all performance, it may be observed that 66% of the starting group lost weight steadily for a period of five weeks or longer.

Weight Loss: The 49 patients who began the formula in the hospital lost an average of 7.3 pounds (range, 1.1 to 13.4 pounds) during the first four days. There was no correlation between the degree of obesity and the initial response to treatment. The group treated entirely in the clinic showed similar results in measurements of lost weight obtained at five- to eight-day intervals after the beginning of formula therapy. The 86 patients who dieted for a month or more showed an average loss of 16.3 pounds (range,

TABLE 3

Weight Loss of Patients on Formula Diet

The figures refer to the number of patients who lost weight in the cited categories. The figures in parentheses express them as a percentage of the starting group of patients.

	Number of Patients Who Lost				Total
	Less than 10 Lbs.	10–19 Lbs.	20–39 Lbs.	40 Lbs. and over	
Those starting with initial hospitalization	5 (10%)	13 (27%)	13 (27%)	18 (36%)	49
Those starting in out-patient clinic	13 (23%)	12 (21%)	17 (30%)	15 (26%)	57
Entire group	18 (17%)	25 (24%)	30 (28%)	33 (31%)	106

9.4 to 30.4 pounds) during the first month. In all cases the loss of weight was more rapid during the first few weeks; later, it slowed but continued steadily as long as the patient maintained the prescribed regimen. The final steady rates ranged from one to three pounds per week, with an average loss of about two pounds per week.

Table 3 classifies the patients according to the number of pounds lost during the period of continuous weight reduction. It shows that 63% of the initially hospitalized patients lost at least 20 pounds, and 36% lost 40 pounds or more. Of those who began treatment in the out-patient clinic, 56% lost at least 20 pounds and 26% lost 40 pounds or more. In the

TABLE 4

"Success" Results for Patients on Formula Diet Using Criteria of Trulson, Walsh and Caso[8]

Initial Weight (lbs.)	Criterion of Success (Minimum Number of Pounds Lost)	Initially-Hospitalized Patients		Patients Treated Exclusively in Clinic		Combined Group	
		No. Successful / No. Starting	Per Cent Successful	No. Successful / No. Started	Per Cent Successful	No. Successful / No. Started	Per Cent Successful
Less than 150	10	0/0	—	1/1	100	1/1	100
151–175	15	1/1	100	6/12	50	7/13	54
175–200	20	6/8	75	12/16	75	18/24	75
201–225	25	7/15	47	4/11	36	11/26	42
226–250	30	7/11	64	5/9	56	12/20	60
Over 250	35	5/14	36	5/8	63	10/22	45
Total		26/49	53	33/57	58	59/106	56

entire group of 106 patients who began the diet, 59% lost at least 20 pounds and 33% lost 40 pounds or more. Five patients each lost more than 90 pounds.

In table 4, the patients are distributed according to the criteria of Trulson, Walsh and Caso,[8] in which "success" is defined as the loss of a specified amount, depending upon the original weight. By these criteria, 53% of the hospitalized group and 58% of the clinic group were "successful."

An important feature of tables 3 and 4 is the demonstration that individuals who began treatment exclusively as out-patients showed weight loss percentages essentially similar to those who had started with a four-day hospitalization. The absence of a significant difference between these two groups indicates that effective treatment with a formula diet did not require a preliminary period of hospitalization.

Comparison with Other Dietary Technics: It is difficult to compare diets on the basis of published reports. Results obviously vary with many factors,

including selection of patients, the length of observation and the criteria used for judging success. Most reports do not give data on the percentage of starting patients who abandoned treatment, and only a few studies have tabulated the levels of weight loss by the fraction of patients who persisted.

TABLE 5

Comparison of Weight Loss in Various Dietary Regimens

Case Series Reported	Dietary Method Employed	Number of Patients	Percentage Who Lost				
			Less Than 10 Lbs.	10–19 Lbs.	20 Lbs. and over	20–39 Lbs.	40 Lbs. and over
Bauman[9]	1200 cal.; occasional thyroid	183*	50	27	23	†	
Fellows[10]	Individual caloric instruction, self-selected diet	294	47	27	26	21	5
Gray and Kaltenbach[11]	900 cal. food diet	314‡	52	20	28	21	7
Osserman and Dolger[12]	Diabetics; 1,000 cal. food diet plus Dexedrine	55	35	36	29	27	2
Munves[13]	Indiv. interviews or groups; 1,200–1,800 cal. diet	48	71	21	8	8	0
Harvey and Simmons[14]	Group sessions; 1,000 cal. diet	290	47	30	23	§	
Young et al.[15]	Nutrition clinic; varied diets	131‖	40	32	28	25	3
Jolliffe and Alpert[20]	1,000–1,400 cal.; citrus juice before meals	73	53	36	11	11	0
Present Series	900 cal. formula diet	106	17	24	59	28	31

The number of patients refers to the total number of patients starting the diet, except as otherwise indicated.

* Those who attended the clinic for less than two months were omitted from this tabulation.

† Eight per cent lost 20 to 25 pounds; 15% lost over 25 pounds.

‡ This number includes 71 patients who stopped the diet in the first month, and 31 who later were dropped because of "noncoöperation."

§ Seventeen per cent lost 20 to 29 pounds; 6% lost 30 to 52 pounds.

‖ One hundred sixty-eight patients actually started on diets; the available figures give results on only 131.

Table 5 summarizes the results of all available studies, listing the total number of patients and the amount of weight lost by various percentages of the starting group. It will be seen that a weight loss of over 20 pounds occurred in 59% of the formula group, as compared to 8 to 29% of the other series. A loss of 40 pounds or more occurred in 31% of the formula patients, compared to 0 to 7% of the patients treated with other methods.

Using the criteria of Trulson, Walsh and Caso,[8] table 6 compares the "success" results of the formula diet group with the only two series in which the recorded data permit this detailed comparison. With the exception of patients whose initial weight was less than 150 pounds, the formula patients in each category lost more weight than did the analogous patients in the other series. Taken as a whole, the formula group had a "success" rating of 56%, more than twice that reported in the other two investigations.

TABLE 6

Comparison of "Success" Results, Using Criteria of Trulson, Walsh and Caso[8] of Formula Diet with Two Other Diets

Initial Weight Group (lbs.)	Criterion of Success (Minimal Number of Pounds Lost)	Nutrition Clinic Group Reported by Young et al.[16]		Formula Diet Group	
		No. Successful / No. Started	Per Cent Successful	No. Successful / No. Started	Per Cent Successful
Less than 150	10	11/25	44	1/1	100
151–175	15	11/36	31	7/13	54
176–200	20	13/47	28	18/24	75
201–225	25	3/22	14	11/26	42
226–250	30	1/15	7	12/20	60
Over 250	35	2/11	18	10/22	45
Total		41/156	26	59/106	56
Total of group reported by Trulson, Walsh and Caso.[8] (Individual weight group categories not listed.)		130/847	23		

The comparisons made in tables 5 and 6 do not take into account possible differences in clinic methods and in selection of patients, but the results do indicate that the effectiveness of the formula diet at least equaled that of the more conventional regimens.

Side-Effects: Many workers in sedentary or active occupations subsisted on 900 calories of formula per day without serious fatigue. Some patients cited "weakness" as a cause for stopping the diet, while others who persisted with treatment claimed greater vigor than before. Some patients noted an inordinate and uncontrollable craving for food, while others reported that the taste and frequent feedings of formula kept them sated. However, in almost all instances an abandonment of the diet and return to natural food seemed to be motivated by monotony and desire for new tastes, rather than by simple caloric drive, since no patient voluntarily increased the allotment of formula.

At the beginning of the diet many patients reported a decrease in frequency of bowel movements to once every three or four days. After several

weeks, with or without additional natural food, the previous frequency usually returned. For those individuals who could tolerate this change in bowel habit, only patience was recommended; for the others, mild laxatives or occasional enemas were prescribed.

Loss of weight occasionally was associated with menstrual changes. Regular periods returned to some women with amenorrhea or irregular menses, while in other, previously regular patients, minor irregularities appeared. Some individuals reported transient gastrointestinal disturbances such as nausea, heartburn, eructation or diarrhea. These complaints generally disappeared after the first few weeks of the diet. A variety of other complaints arose, but their brevity and inconsistency of appearance made it difficult to attribute them to the diet.

No new major psychic problems were detected, despite occasional reports [16–18] that reduction of weight can precipitate psychologic crises. In two cases, preëxisting neuroses were sufficiently exacerbated during the diet to warrant psychiatric referral. In general, however, patients who persisted with the diet appeared to be content. The rapid and continuing weight loss in this group encouraged them to continue treatment.

Post-Reduction Maintenance: Table 7 summarizes data on the 12 individuals who reduced to standard weight, and on an additional 36 patients who lost more than 30 pounds. The patients who arrived at their target weights were instructed to approach a maintenance diet by taking formula at the rate of 1,200 calories daily for several days, and then to return to natural food diets of their own selection, beginning at a level of 800 to 1,000 calories. No specific recommendations were made, other than to emphasize the need for adequate caloric restriction, since most patients were quite familiar with natural food diets and calorie-counting. They were advised to continue on a restricted diet for several months, if necessary, and then to make gradual increases in the amount of food.

In almost all cases the resumption of natural food was followed by an immediate gain of from three to six pounds—probably a return to the extracellular space of fluid lost at the beginning of the diet. In anticipation of this response, patients nearing the completion of treatment were advised to reduce to about six pounds below the weight selected as a final goal.

The data in table 7 indicate the unequal success of patients in maintaining themselves in the reduced state. During the first year after reduction, six of the 12 patients who had achieved normal weight gained back 30% or more of the lost weight. Of the group of 36 patients who lost over 30 pounds, adequate follow-up data are available on 26. Of these, 14 (54%) regained 30% or more of their lost weight. The 18 patients from both these groups who managed to limit the return of weight to 30% or less reported the need for constant dietary vigilance. Several of them found it necessary to continue with a daily food intake of 800 to 1,000 calories for many months. Others found that episodes of dietary excess, with conse-

TABLE 7

Individual Data on Patients Who Achieved Normal Weight and on Others Who Lost More Than 30 Pounds

Patient	Age Sex	Occupation	Initial Wt. (lbs.)	Standard Wt.* (lbs.)	Amt. Over-Wt. (lbs.)	Weeks of Wt. Reduction	Wt. at End of Reduction (lbs.)	Wt. Lost (lbs.)	Follow-Up Period			
									Time After Beginning of Formula Diet (mos.)	Wt. at Time of This Report (lbs.)	Amt. of Wt. Regained (lbs.)	Per Cent of Lost Wt. Which Has Been Regained
I. Patients who reduced down to or below standard weight												
L. A.	54 M	Dentist	218	177	41	8	175	43	15	176	1	2
B. B.	43 F	Housewife	179	136	43	22	137	42	14	144	7	17
W. C.	61 M	Janitor	222	169	53	19	162	60	15	198	36	60
A. F.	32 M	Swimming Instructor	184	162	22	10	152	32	15	175	23	72
D. G.	36 F	Secretary	201	160	41	23	156	45	14	172	16	36
V. P.	52 F	Sales Clerk	157	139	18	6	137	20	14	149	12	60
M. S.	48 F	Housewife	198	148	50	18	144	54	12	158	14	26
V. S.	18 F	Student	166	136	30	14	127	39	13	148	21	54
M. V.	55 F	Nurse	195	159	36	20	149	46	13	151	2	4
C. W.	23 F	Housewife	188	138	50	23	131	57	14	152	21	42
R. Z.	59 F	Housewife	200	134	66	55	134	66	18	144	10	15
E. Z.	25 F	Housewife	231	134	97	34	120	111	14	143	23	21
II. Patients who lost more than 30 pounds, without reaching standard weight: A. Initially hospitalized												
J. C.	48 F	Governess	233	134	99	41	145	88	Follow-up not available			
I. C.	40 F	Housewife	292	134	158	35	254	38	16	270	16	42
C. C.	33 F	Machinist	212	128	84	29	163	49	15	177	14	29
D. C.	47 F	Housewife	233	145	88	36	188	45	16	195	7	19
A. C.	26 F	Housewife	172	119	53	25	130	42	16	137	7	17
R. G.	21 F	Secretary	292	131	161	16	258	34	Subsequent weight-loss upon re-admission to hospital			
S. G.	39 M	Salesman	267	169	98	26	190	77	15	229	39	51
R. K.	40 F	Housewife	380	133	247	36	275	105	14	277	2	2
R. K.	34 F	Housewife	249	141	108	45	192	57	14	192	0	0
J. L.	22 F	Student	205	125	80	17	162	43	Subsequent weight-loss upon re-admission to hospital			

TABLE 7—(*Continued*)

TABLE 7—(*Continued*)

Patient	Age Sex	Occupation	Initial Wt. (lbs.)	Standard Wt.* (lbs.)	Amt. Over-Wt. (lbs.)	Weeks of Wt. Reduction	Wt. at End of Reduction (lbs.)	Wt. Lost (lbs.)	Follow-Up Period			
									Time After Beginning of Formula Diet (mos.)	Wt. at Time of This Report (lbs.)	Amt. of Wt. Regained (lbs.)	Per Cent of Lost Wt. Which Has Been Regained
A. Initially hospitalized—(*Continued*)												
N. M.	31 F	Unemployed	351	137	214	35	240	111	14	262	22	20
H. M.	51 M	Executive	232	133	99	24	155	77	15	188	33	43
A. M.	44 F	Housewife	241	142	99	31	205	36	15	209	4	11
P. R.	33 F	Secretary	180	138	42	13	146	34	14	176	30	88
E. R.	45 F	Housewife	355	139	216	9	323	32	Follow-up not available			
B. W.	35 M	Machinist	244	141	103	16	207	37	15	244	37	100
C. W.	36 F	Unemployed	303	140	163	14	259	44	14	251	−8	−18
H. W.	25 F	Housewife	250	136	114	24	182	68	Follow-up not available			
B. Treated exclusively in Out-patient Clinic												
P. A.	17 F	Student	192	125	67	32	149	43	Follow-up not available			
C. A.	20 F	Student	179	114	65	23	146	33	12	150	4	12
A. B.	42 F	Housewife	190	141	49	20	153	37	Follow-up not available			
L. B.	33 F	Beautician	308	152	156	30	259	39	Follow-up not available			
S. B.	18 F	Student	218	132	86	7	180	38	8	235	55	145
D. F.	52 M	Meat Broker	266	187	79	9	221	45	14	236	15	33
D. F.	45 F	Housewife	200	134	66	32	168	32	Follow-up not available			
Y. G.	44 F	Housewife	245	142	103	9	210	35	14	229	19	54
C. L.	32 F	Teacher	197	122	75	31	165	32	14	161	−4	−13
E. M.	27 F	Housewife	232	134	98	29	173	59	14	177	4	7
R. M.	15 M	Student	231	139	92	11	185	46	14	206	21	46
E. M.	25 F	Housemaid	209	127	81	27	153	56	12	177†	18	32
P. R.	46 F	Singer	226	151	75	16	181	45	14	200	19	42
L. R.	54 F	Teacher	206	147	59	17	172	34	Follow-up not available			
N. R.	45 M	Taxi-driver	376	149	226	61	226	150	14	226‡	0	0
A. S.	44 F	Realtor	256	136	120	28	161	95	14	225	64	67
E. W.	30 F	Secretary	280	144	136	23	234	46	13	257	23	50
J. W.	42 F	Secretary	186	146	40	23	147	39	16	167	20	51

* Using standards of 1912 Life Insurance Survey.
† Pt. seven months pregnant at time of this weighing.
‡ Pt. still undergoing active weight reduction.

quent gains in weight, could be counteracted by returns to the formula diet for two- or three-day periods. A number of individuals reported that their long period of food deprivation had left them with a diminished desire for food and a lower satiety threshold, while others reacted to liberation from the formula with such a huge intake of food that their weights rose above the initial level.

Serum protein concentration, hemoglobin and hematocrit values, measured in 13 patients after the loss of 32 to 150 pounds of weight, remained within normal limits. Liver function tests in this group showed only minor variations from normal (table 8), and these were limited to patients who

TABLE 8

Hemoglobin, Serum Protein and Liver Function Test Results in Patients on Maintenance Diets Following Weight Reduction with Formula Diet

Patient, Age, Sex	Wt. Lost during Active Reduction (lbs.)	Duration of Active Wt. Reduction (wks.)	Interval Elapsed since Cessation of Formula Diet (mos.)	Wt. at Time of Tests (lbs.)	Total Serum Protein (gm. %)	Serum Albumin (gm. %)	Hemoglobin (gm. %)	Serum Bilirubin (mg. %)	45 min. BSP Retention (%)	Cephalin Flocculation	Thymol Turbidity (units)
L. A. 54 M	43	8	13	176	7.2	4.8	14.5	0.6	1.0	0	0
B. B. 43 F	42	22	9	144	7.0	4.5	13.2	0.35	1.0	0	0
R. K. 40 F	105	36	6	277	7.4	4.6	13.0	0.5	1.5	0	4.0
R. K. 34 F	57	45	5	192	6.5	5.0	13.3	0.7	1.0	0	1.0
C. L. 32 F	32	31	7	161	6.6	4.7	13.6	0.7	3.5	0	2.0
E. M. 27 F	59	29	7	177	7.0	5.0	13.0	0.5	0.5	0	0
N. M. 31 F	111	35	6	262	7.6	4.1	13.0	0.35	5.5	0	0
N. R. 45 M	150	61	0	226	6.85	4.2	12.9	0.5	10.0	0	1.0
A.S. 44 F	95	28	8	225	6.6	4.2	13.4	0.75	5.0	0	1.0
M. V. 55 F	46	20	9	151	7.0	4.6	13.7	0.6	1.5	0	1.0
J. W. 42 F	39	23	11	167	7.2	5.0	13.2	0.7	3.5	0	3.0
R. Z. 59 F	66	55	6	144	7.0	4.8	13.0	1.0	1.0	0	2.0
E. Z. 25 F	111	34	7	143	6.5	4.3	13.4	0.6	1.0	3+	1.0

were still obese despite considerable loss of weight. The findings confirm those of Zelman, [19] who showed that various abnormalities of liver function, especially retention of bromsulfalein, can be detected in patients with uncomplicated obesity.

Discussion

Many intangible factors play significant roles in the successful outcome of any reduction diet. Without question, the physician himself is a therapeutic agent. The enthusiasm with which he approaches his task, and the attention and support he gives the patient, are probably as important as any specific features of a prescribed diet. Careful attention to the psychologic and physiologic problems of the dieting patient, frequent clinic visits, and the regularity of follow-up visits once weight reduction is achieved are essential to the value of any dietary regimen.

In the present study the patients were seen by a single interested physician at weekly or bi-weekly intervals. All services were free, and regular evening clinics were available to those who could not attend during the day. The patients were a motivated group in that all had come to the clinic prepared to diet. Many were extraordinarily obese, desperate about their previous failures at weight reduction, and anxious to try a new form of treatment.

It is apparent, however, that certain intrinsic features of the formula diet contributed to its effectiveness. The outstanding and perhaps the only advantages of formula feeding are simplicity and inflexibility. The patients taking formula had no complex food lists from which to decide what and how much to eat. Any violation of the dietary prescription was unmistakable. For many patients this rigidity was useful, since it removed uncertainties and self-deception in estimating the caloric values of natural foods. Moreover, many patients reported that they found total abstinence from natural foods more tolerable and less frustrating than previous attempts at limitation of quantity.

For the physician, the ease with which the formula diet could be prescribed and administered appeared to be a practical advantage. Using a formula, the physician could prescribe a single, quantitatively defined nutrient mixture of any chosen proportions and assure the patient of a predictable weight loss as long as the diet was followed. Dietary departures, when they occurred, could be discussed without cumbersome food charts and tables of caloric values with a patient who was fully aware of the existence and quantity of his dietary indiscretions.

It must be emphasized, however, that a formula diet deals with only the initial phase in the total management of an obese patient. It is a safe and effective method for losing weight, but it alone does not produce the basic and permanent changes of eating and exercise habits which are required for ultimate success with any weight-reduction program. After reduction has

been accomplished, the formula feeding must be replaced by a mixture of conventional foods adjusted for maintenance of the patient at the reduced weight.

Summary

One hundred six obese out-patients, of an average weight of 224 pounds, were given a 900-calorie food diet, composed of evaporated milk, dextrose, corn oil and water, supplemented by a multivitamin capsule. The patients were seen in the out-patient clinic at weekly or bi-weekly intervals. Many patients made satisfactory adjustments to the practical problems of taking a formula diet. None of them showed any clinical signs of nutritional deficiency.

Fifty-three per cent of those who began treatment lost over 20 pounds; 28% lost over 40 pounds. One year later it was found that 46% of the patients who had lost 30 pounds or more had been able to limit the regaining of weight to less than 30% of the original loss. It was concluded that formula feeding can be a useful adjunct of a weight-reduction program. Like any other reduction diet, it is but a transitional measure, dealing with the first stage of treatment.

Summario in Interlingua

Cento sex obese patientes visitante de un peso medie de 224 libras esseva instruite in le uso de un dieta de 900 calorias per die le qual permitteva nulle ingestion de alimentos natural sed in le qual le sol fonte de nutrientes esseva un mixtura a formula fixe consistente de lacte evaporate, dextrosa, oleo de mais, e aqua. Le mixtura esseva preparate per le patientes a lor domicilios e prendite in cinque o sex portiones diurne. Illo esseva supplementate per capsulas multivitaminic. Liquidos noncaloric esseva permittite al discretion del subjectos individual. Nulle adjuncte medication pro reduction de peso esseva usate. Le patientes esseva re-examinate al clinica a intervallos septimanal o bi-septimanal.

Dece-cinque pro cento del patientes succedeva a observar le dieta scrupulosemente durante plus que 11 septimanas, 7% durante plus que 21 septimanas. Ben que 56% del patientes comenciava prender altere alimentos intra le prime duo septimanas, quasi un medietate de istes succedeva a confinar los a un modeste supplemento al basic ration diurne del mixtura prescribite. Illes continuava le curso del regime dietari e obteneva un progressive reduction de peso. In le casos in que le regime esseva mantenite fidelmente, le perdita de peso amontava a inter 12 e 20 libras durante le prime mense e a inter un e tres libras per septimana durante le periodo subsequente.

Datos reportate pro altere regimes de reduction de peso indica que inter 8 e 29% del patientes comenciante varie planos pro le reduction de lor peso succedeva a perder 20 libras o plus, e inter 0 e 7% perdeva 40 libras o plus. Sub le conditiones del plano hic reportate, 59% del patientes perdeva 20 libras o plus, 31% perdeva 40 libras o plus, e cinque del individuos perdeva plus que 90 libras. Nulle significative manifestationes clinic o laboratorial de deficientias nutritional esseva incontrate in ulle del patientes. In le casos ubi un peso normal esseva effectuate, le retorno a alimentos natural esseva complite sin difficultates digestive, sed un constante vigilantia dietari esseva necessari pro evitar le reaccumulation del peso perdite.

Un anno plus tarde, il esseva trovate que 46% del patientes qui habeva perdite 30

libras o plus habeva succedite a restringer le reaccumulation de peso a minus que 30% del perdita original.

Le principal disadvantage del dieta e le plus frequente causa de su abandono esseva su monotonia. Ben que le optime surveliantia clinic possibile contribueva significativemente al successo del regime, certe aspectos intrinsec del dieta esseva etiam de grande importantia. Le prime e principal inter istos esseva le simplicitate e inflexibilitate del dieta. Il esseva evidente que multes del patientes prefereva abstiner se completemente de alimentos natural a deber occupar se del complexitates de contar calorias in seliger inter varie alimentos o a deber suffrer le frustration de restringer le ingestion de alimentos permittite a illes e formante un parte de dietas conventional.

Le composition del formula dietari usate in le presente studio non es considerate como essential pro iste typo de dieta. Mixturas de altere composition, sed equalmente restringite in le numero de lor calorias, ha producite simile resultatos in studios preliminari con patientes hospitalisate o remanente a lor domicilios.

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PLEURAL BIOPSY AS AN AID IN THE ETIOLOGIC DIAGNOSIS OF PLEURAL EFFUSION: REVIEW OF THE LITERATURE AND REPORT OF 132 BIOPSIES*

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Introduction

The inability of the physician to establish rapidly and accurately the etiology of pleurisy with effusion has been recognized for many years. As a result of experience, based mainly on observation, coupled with a statistical analysis of the results of the more commonly accepted diagnostic technics, certain adages and rules of thumb have become axiomatic. In general, these assumptions have withstood years of bombardment in from 70 to 80% of the cases, but the application of these principles to the remaining 20 to 30% has occasionally been associated with increases in morbidity and mortality. Recently, with the introduction of improved methods of therapy for those effusions of tuberculous etiology and innovations and advancements in the treatment of effusions due to causes other than tuberculosis, the importance of rapidly establishing an etiology has been highlighted.

With the recognition of the limitations of the available diagnostic technics, and the realization that the demand for additional and/or more accurate methods was of paramount importance, direct tissue examination of the diseased pleura by means of biopsy was an inevitable development. A review of the literature of the use of biopsy and a study of 132 cases of parietal pleural biopsy constitute the basis for this report.

Review of the Literature

Although biopsy of the diseased pleura was frequently undertaken during thoracotomies which were performed for therapeutic indications, it was not until recently that direct biopsy of the diseased pleura performed specifically for diagnostic purposes was undertaken and reported.

Lloyd [1] in 1953 reported the use of thoracoscopy (a procedure which had apparently been practiced in Europe for years), supplemented by biopsy in 16 of 23 patients. In 12 a histologic diagnosis was obtained, in four

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pleural biopsy was unsuccessful, and in the remaining seven it could not be performed. He emphasized that this procedure was of extreme value in differential diagnosis, and encouraged its use despite numerous obvious theoretic and practical contraindications.

Sutliff, Hughes and Rice [2] utilized biopsy of the pleura employing partial rib resection without exploration in 21 selected cases of persistent pleural lesions. All of their cases had originally had pleurisy with effusion, and the biopsies were performed anywhere from two to 11 months after the onset. None, however, was thought to have free pleural fluid present at the time of biopsy. All cases with obvious pulmonary lesions were thought to have been excluded, and no etiology had been established in any case. All of the patients had biopsies before the introduction of isoniazid (INH), and most even before streptomycin and para-aminosalicylic acid (PAS) were routinely employed. Histologic diagnoses were obtained in 20 of their 21 cases.

In 1955 Small and Landman [3] reported the use of pleural biopsy in five cases, employing the procedure as recommended by Klassen during lung biopsy, which requires no rib resection and is therefore easier to perform. Three of their patients presented diagnostic problems only, but in the other two biopsy was performed at thoracotomy which was undertaken for other reasons.

In the same year Stead, Eichenholz and Stauss [4] published the results of thoracotomies performed on 24 patients with the syndrome of idiopathic pleurisy with effusion. In addition to the histologic results obtained from the pleura, they contributed significant information about the underlying lung, the pleural space and associated bacteriologic studies. Interestingly enough, the indications for thoracotomy in this group of patients was either a therapeutic one—specifically, decortication or resection of residual parenchymal lesions—or diagnostic, i.e., patients in whom some feature of the illness suggested that they did not conform to the usual clinical picture of idiopathic exudative pleurisy. This latter indication was adequately justified when it was discovered that, in truth, nine of the 24 patients had no evidence of tuberculous involvement. The procedures were performed at varying intervals of treatment, with a mean of eight months.

DeFrancis, Klosk and Albano [5] were the first to report histologic changes in the pleura obtained by needle biopsy from patients with active tuberculous effusions. They described in some detail the technic of aspiration biopsy utilizing a Vim-Silverman needle. Evidence of granulomatous pleuritis was obtained in two patients, and the authors indicated that the procedure had been employed in a total of six patients, although no etiologic diagnoses were mentioned in the other four cases.

In February, 1956, Heller, Kellow and Chomet [6] reported their results in 20 cases of pleural effusion obtained by aspiration biopsy. They subsequently published these,[7] in addition to five other cases in whom surgical

biopsy was employed. They emphasized that aspiration biopsy was a useful technic in the differential diagnosis of pleural effusions.

Simultaneously, Breckler and his colleagues [8] studied 16 consecutive patients who presented either with active pleural effusions or with evidence of residual pleuritis. Surgical biopsy was employed in all cases and was helpful in 10, of which nine were tuberculous and one malignant. They indicated that in some patients a nontuberculous etiology had been established prior to biopsy, although no studies performed prior to biopsy in the patients with tuberculosis were discussed. In addition, they indicated that aspiration biopsy had simultaneously been performed in the first five cases, but had been subsequently abandoned, since in their series the surgical procedure was no more difficult and the results were far superior.

Douglass, Carr and Bernatz [9] recently reported their results in the use of diagnostic thoracotomy and pleural biopsy in a group of 21 patients studied over the last 15 years. As in most previous reports, at the time of biopsy or exploration the effusion or pleuritis had been present on the average of seven months, although the duration ranged from two weeks to three years. All other conventional diagnostic procedures had been employed without benefit. They were able to establish an etiology definitely in 12, and demonstrated nonspecific inflammatory changes due to various causes in seven; in only two were they unable to establish any specific cause. However, they also concluded that early diagnosis in pleural effusion is imperative. They further indicated that it seems unwise in many cases to burden a patient with the various socio-economic and therapeutic implications attendant upon a diagnosis of tuberculosis when proof has not been established.

More recently we [10] reported results obtained utilizing aspiration biopsy as a diagnostic aid in 45 cases of active pleural effusion. In all cases the biopsy was performed *early* in the course of the illness, an average of one week after admission to the hospital. The diagnosis had been established by other means in only one case prior to biopsy, and in 33 of the 45 cases so studied, pleural tissue was obtained. We commented also on the interpretation of reports of nonspecific inflammation, and the implications attendant upon such a diagnosis. Twelve of our 45 cases were "unsuccessfully" biopsied, i.e., we considered the tissue obtained not truly representative of pleural tissue. Earlier [11] we had suggested that if either of the above findings was obtained (pleura with nonspecific inflammatory changes, or "pleural fibrosis"), a repeat aspiration biopsy or a surgical biopsy was indicated. This resulted from experience in demonstrating tuberculosis and malignancy at subsequent thoracotomy in patients whose pleural biopsies were not diagnostic. Other investigators [6, 8] have since included fibrosis as definitely representing pleura, but also question its value.

We further recommended that aspiration biopsy be performed in every case of pleural effusion where the diagnosis was not readily apparent, and

that it be carried out at the time of the first thoracentesis. We thought it represented a safe, quick, early method of diagnosis which was far superior to any currently available method.

The histologic results and type of procedures employed in all of these reported studies are listed in table 1. It is interesting to note that in many cases biopsy was accomplished at the time of thoracotomy, performed for either diagnostic or therapeutic reasons. Granulomatous pleuritis was the most common histologic finding. In every series except three (one of which only included two cases) pleura demonstrating only nonspecific changes was a frequent finding. The implications to be derived are numerous: (1)

TABLE 1

Pleural Biopsy

(Summary of Previously Reported Results)

Author	No. of Cases Reported	Method Employed	Biopsy Specific	Indication	Tissue Diagnosis					
					Gran.	Mal.	NSP	Misc.	Normal	Inadeq.
Lloyd[1]	23	Thoracoscopy with biopsy	12	Diagnostic	0	12	0	0	0	4
Sutliff et al.[2]	21	Surgical with rib and exploration	20	Diagnostic	17	2	1	1	0	0
Small and Landman[3]	5	Surgical without exploration	5	Diagnostic and therapeutic	5	0	0	0	0	0
Stead et al.[4]	5 24	Surgical with full exploration and lung biopsy	15	Diagnostic and therapeutic	15	0	9	0	0	0
DeFrancis et al.[5]	6	Aspiration	2	Diagnostic	2	0	0	0	0	4
Heller et al.[6,7]	20	Aspiration	9	Diagnostic	5	4	9	0	0	2
	5	Surgical	2		2	0	2	1	0	0
Breckler et al.[8]	16	Surgical	10	Diagnostic	9	1	6	0	0	0
Douglass et al.[9]	21	Surgical	11	Therapeutic and diagnostic	5	6	7	3	0	0
Donohoe et al.[10]	45	Aspiration plus surgical when required	25	Diagnostic	14 5	4 2	13 2	1 0	1 0	12 0

Gran. —Granuloma.
Mal. —Malignancy.
NSP —Nonspecific pleuritis.
Misc. —Miscellaneous.
Normal—Normal.
Inadeq.—Inadequate.

biopsy can be helpful only when specific changes can be demonstrated in the tissue removed; (2) the area biopsied may not truly reflect the histologic changes of the entire organ, and therefore false-negative results may be obtained in either the aspiration method or the surgical method if full exploration is not employed; (3) even though biopsy helps to reduce the number of indeterminate cases of pleurisy with effusion, and should therefore be employed more frequently it is still necessary in a small group without a specific diagnosis to continue to pursue etiologic factors and to observe the patient; and (4) a patient with a pleural effusion should not be subjected to long-term treatment for tuberculosis without either bacteriologic and/or histologic proof.

Therefore, if conventional methods fail to uncover tubercle bacilli, and

if aspiration biopsy yields either nonspecific pleuritis or "pleural fibrosis," we feel a surgical biopsy (of the Klassen type) should be employed. If a frozen section is not more specific, then full thoracotomy with exploration is recommended.

Clinical Material and Method of Study

There were 111 patients in the study, of whom 83 were males and 28 females. Eighty-six were Negroes, 24 were white and one was an Oriental. The youngest patient was 13 and the oldest 83.

One hundred thirty-two biopsies in these 111 patients were performed, 78 of the aspiration type and 54 utilizing surgical methods. Thirty-three of the 54 had only the surgical approach, whereas 21 had previously had aspiration biopsy. Surgical biopsy was necessitated either because of inadequacy of the specimen obtained by aspiration biopsy (seven cases) or, more often, because of the histologic finding of nonspecific pleuritis (14 cases). Twenty-seven of the 33 patients in whom only surgical biopsy was performed were studied prior to the use of aspiration biopsy. The other six had a contraindication to aspiration biopsy—specifically, no free fluid obtainable at thoracentesis. The indication for biopsy in every case was diagnostic, and in only two patients had an etiology been established by other methods.

All cases of pleural effusion included in the aspiration biopsy group were categorized into three broad groups, based on an early clinical appraisal: group I consisted of patients in whom tuberculosis was thought to be the most probable cause; group II consisted of those in whom the suspicion of malignancy was predominant, and group III represented an indeterminate group of patients in whom no etiology was readily apparent, or in whom some features of the illness—historical, clinical or radiographic—were present which prevented definite classification as either tuberculous or malignant. All patients were purposely excluded if the cause of pleural fluid was readily apparent, whether it was congestive heart failure, empyema, infarction, trauma, cirrhosis, postpneumonic serous effusion or spontaneous pneumothorax with hemothorax.

In the 78 patients in whom the aspiration method was utilized, biopsy was performed either on admission at the time of the initial thoracentesis, or within the first 10 days of hospitalization. Biopsy at this early stage, however, was not applicable to the surgical group, for several obvious and distinct reasons: first, 21 were performed after the results of aspiration biopsy had proved to be either inadequate or inconclusive; second, 27 had been biopsied prior to the use of the aspiration technic, and in most cases surgical biopsy was delayed because of toxicity and/or to await the results of the conventional diagnostic studies; and third, in the remaining six a short period of observation was allowed to see whether more fluid would develop. Further delay was encountered since the surgical procedure, although not

TABLE 2

Results of Aspiration Biopsy Performed in 78 Patients with Pleural Effusion

	Clinical Impression	No. of Cases	Gran.	NSP	Mal.	Norm.	Inad.
I	Tuberculosis	38	20(52.6%)	12(31.5)	0	0	6(15.9)
II	Malignancy	19	0	7(36.8)	8(42.1)	1(5.5)	3(15.6)
III	Indeterminate	21	2(9.6)	10(47.6)			9(42.8)
	Totals	78	22(28.2)	29(37.3)	8(10.3)	1(1.1)	18(23.1)

Gran. —Granulomatous.
NSP —Nonspecific pleuritis.
Mal. —Malignancy.
Norm.—Normal.
Inad. —Inadequate.

a major one, requires the scheduling of the surgeon, the operating room and the anesthetist.

The histologic results in the aspiration group are listed in table 2. Of 78 patients studied, pleural tissue was obtained in 60 (77%). In the remaining 18 patients, various types of tissue were reported, most commonly skeletal muscle, with or without connective or fibrous tissue which demonstrated evidence of inflammation. As previously described,[10] we feel that one surface of the specimen must contain evidence of mesothelial cells to be labeled as pleural tissue. However, both Heller and Breckler [6, 8] include this type of tissue as pleural (although they do question its value). That it may represent pleura cannot be denied. The inability to obtain pleura by aspiration needle biopsy depends upon the following factors: the experience of the individual performing the biopsy, the amount of free fluid present, the thickness of the pleura and the fibrinous peel, and the number of specimens obtained. Most of our failures occurred early in the study; in over 50% of these free fluid was not present, in all but five only one biopsy was performed, and in four the fibrinous peel was marked.

TABLE 3

Fate of 18 Patients in Whom Aspiration Biopsy Yielded Inadequate Results

		Open	Result	Comments	
				Both Alive and Well	Other Proof
Group I	6	4	3 TBC 1 NSP	2	Both had + bact.
Group II	3	0		All had contraindications to surgery. All 3 are dead; 2 had autopsy confirmation of malignant pleural involvement and in the other the clinical course was compatible.	
Group III	9	3	3 NSP	Four died and all were autopsied, with three showing NSP and one normal pleura. Two are alive and unchanged, one has lupus, one had multiple septic emboli.	

Only seven of the 18 patients in whom inadequate tissue was obtained underwent surgical biopsy, and those results are listed in table 3. The others either had obvious contraindications to open biopsy or refused the procedure. However, in all cases the clinical impression was confirmed by other methods (clinically, bacteriologically or post mortem).

Of the total of 29 patients in this group in whom aspiration biopsy yielded a tissue diagnosis of nonspecific inflammation, 14 were subjected to open surgical biopsy, with or without total exploration (table 4), and

TABLE 4

Fate of 29 Patients in Whom Nonspecific Pleuritis Was Obtained by Aspiration Biopsy

	Surgical Biopsy, with or without Exploration				Comments
	No.	Results			
		G	NSP	Mal.	
Group I	9	5	3	1	Two not treated for TBC and alive and well. Required exploratory.
II	2	0	0	2	
III	3	0	3	0	
Totals	14	5	6	3	

Probable cause for nonspecific pleuritis in 15 cases in whom biopsy not done.

Group I	3	Two had other proof of tuberculosis, one tissue and one bacteriologically. One walked out before adequately studied.
Group II	5	All five had malignant invasion of pleura, three proved by other histologic methods and two at autopsy.
Group III	7	One awaiting open. Four under observation and asymptomatic. One lost to study. One dead with nonspecific pleuritis at autopsy, with only chronic heart failure demonstrable as the cause.

the remaining 15 either refused the procedure or had obvious contraindications. The diagnosis in the latter group was confirmed subsequently by other methods in all but two, and these were inadequately studied (table 4). Complications, which occurred in only three cases, consisted of small localized areas of pneumothorax that required no special therapy.

RESULTS

Effusions Due to Tuberculosis: Group I. This group consisting of those in whom the clinical impression of tuberculosis was paramount, as represented radiographically by evidence of an effusion but no parenchymal lesion, included 38 patients. Pleural tissue was obtained by aspiration biopsy in 32 (84%), and inadequate tissue in six cases. Of the 32, evidence of granulomatous involvement, with or without caseation, was demonstrable

in 20 (figure 1), and nonspecific pleuritis was found in the remaining 12 (figure 2). Of these, nine were subjected to surgical biopsy. Granulomatous changes were present in five, one had metastatic adenocarcinoma, and nonspecific findings were corroborated in the other three. In the remaining three patients with nonspecific pleuritis, one had bacteriologic proof of tuberculosis by cultures, one had other histologic evidence of tuberculosis, and one left the hospital against advice before complete studies could be performed.

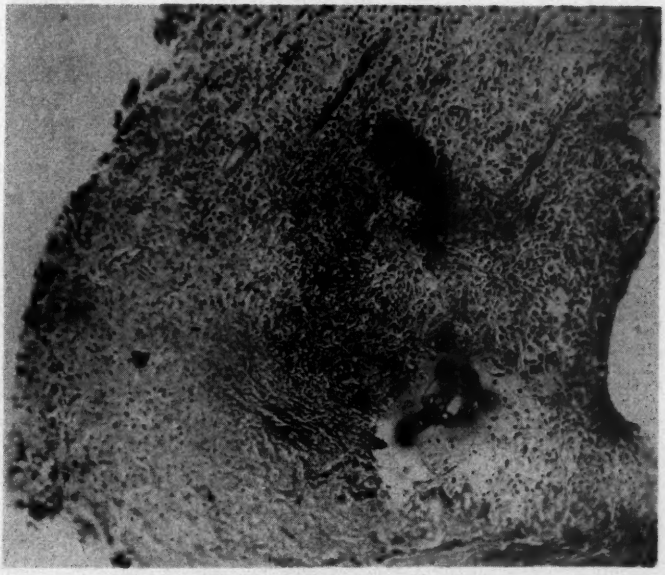

FIG. 1. Histologic section obtained by aspiration biopsy in a 35 year old Negro male with pleural effusion which demonstrates a caseating granuloma.

Of the six patients in this group in whom the aspiration biopsy was unrewarding, three were found to have a caseating granulomatous pleuritis at surgical biopsy. A fourth had only nonspecific inflammatory changes, but subsequently tubercle bacilli were demonstrated on culture of gastric washings on six occasions. Furthermore, as the pleuritis cleared a parenchymal lesion, radiographically consistent with a tuberculous infiltrate, was demonstrable, and the course was subsequently compatible with pulmonary tuberculosis. The other two patients refused surgical biopsy, but subsequently tubercle bacilli were repeatedly cultured from the sputum.

To summarize this group, pleura obtained at biopsy either by aspiration or surgically was found to have granulomatous changes consistent with tuberculosis in 28 of 38 patients (73%). It was the earliest proof of the etiology in all but two of these, and the *only* evidence in 19. Tuberculosis

was established as the cause of pleural effusion in five other cases through bacteriologic and/or histologic proof; one of these had nonspecific changes in the pleura, and in the other four no biopsy was performed. Three of the remaining five patients were found to have nonspecific inflammatory changes in the pleura despite repeat open surgical biopsy. , None was treated for tuberculosis, and after varying periods of observation these patients are

FIG. 2. Photomicrograph of a specimen of pleura obtained by aspiration technic in which only chronic nonspecific inflammation is demonstrable.

still asymptomatic and have normal roentgenograms. One patient was not adequately studied before he walked out, and may or may not have had tuberculous pleurisy with effusion; the fifth had metastatic carcinoma.

Group II. Effusions Due to Malignant Growth: Nineteen patients were listed in this group as having effusions of malignant origin on the basis of their history, clinical course and x-rays. As in the previous group, no etiology had been ascertained prior to biopsy.

Pleural tissue was obtained in 16 (84%) and inadequate tissue in three patients subjected to aspiration biopsy utilizing the Vim-Silverman needle. It is significant, however, that of the 16, malignant involvement was found in only eight (figure 3), nonspecific changes were seen in seven, and a normal pleura was found in one. All 19 patients, however, were subsequently proved to have malignant lesions through other methods (tables 3 and 4). Of the seven patients in whom nonspecific changes were found via aspiration biopsy, two were subjected to open biopsy with full exploration

and bronchogenic carcinoma was discovered. Of the remaining five, not all of whom were candidates for an open procedure, two had malignant lesions demonstrable at postmortem examination. Of the other three, one was found to have typical malignant cells obtained at aspiration biopsy of a lung mass which was demonstrable when the fluid had been removed, and the others had subsequent pleural fluid aspirated which yielded malignant cells. The patient in whom normal pleura had been obtained also had postmortem evidence of malignancy. In three of the four patients in whom

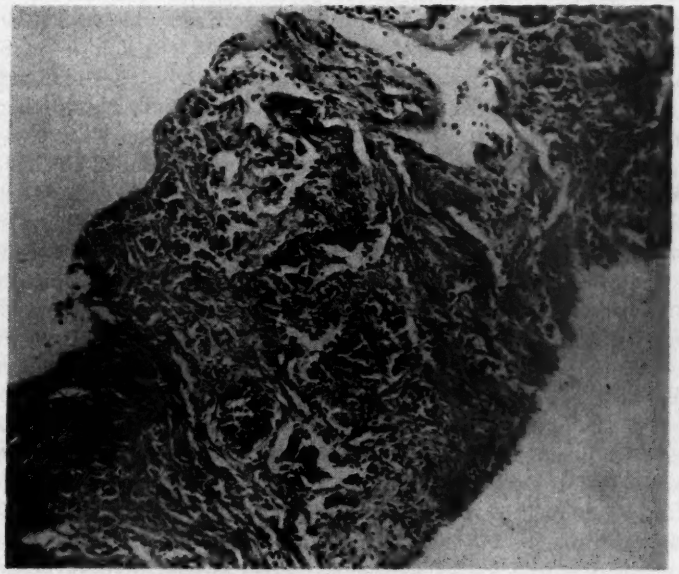

FIG. 3. Malignant invasion of the pleura in a 55 year old Negro female with carcinoma of the breast. This specimen was also obtained by needle biopsy.

autopsy was performed, small isolated implants were found scattered on the parietal pleural surface, so that it was entirely conceivable—and even likely—that the small aspiration biopsy would have missed the area of malignant involvement. This phenomenon was actually demonstrated in one patient.

Of the remaining three patients in this group, those in whom aspiration biopsy yielded inadequate tissue, all subsequently died within a three-month period, and malignant lesions were demonstrable at postmortem examination in two. In the case of the third patient, permission for postmortem examination was not obtained, but the clinical course was compatible with malignant invasion, and although repeat biopsy was not performed, cell block performed on subsequent pleural fluid also yielded typical malignant cells.

In summary, then, of the 19 patients, pleural biopsy demonstrated ma-

lignant changes in 10 (slightly over 50%). Five of the remaining nine had changes consistent only with chronic inflammation, one had normal pleura, and three had inadequate specimens, although subsequently all had confirmation of malignancy. Eight of the 19 patients could be said to have had false-negative biopsies, for in truth, malignant involvement of the pleura was established to be present in all. The time element must be considered in respect to the above conclusion, since it is conceivable, although conjectural, that at the time of biopsy only nonspecific changes were present. This same thought has been suggested by others,[1] who feel that all bloody malignant effusions were probably serous at one time. However, the most commonly accepted theory of the pathogenesis of effusion in malignant lesions is actual pleural invasion through metastases, so that malignant invasion was probably present at the time of the biopsy, and these do, therefore, represent false-negatives.

Group III. Effusions of Indeterminate Cause: Included in this group were 21 patients in whom no obvious cause was discernible from the history and clinical course. Pleural tissue was obtained in only 12, by far the poorest yield of all groups. Significantly, however, of the nine patients from whom pleural tissue was not obtained, only four had free fluid present; the other five had either residual pleuritis or small areas of loculated fluid, both of which factors significantly lower the possibility of obtaining pleural tissue.[10] In addition, aspiration biopsy was performed on only one occasion in all but two, another cause for a lower percentage.

Of the 12 patients from whom pleura was obtained, granulomatous changes were demonstrable in two and changes of nonspecific inflammation were present in 10, one of whom had a marked eosinophilic invasion. Of the latter 10, only three had thoracotomy. The same nonspecific changes were demonstrable in the pleura, pericardium and lung in one, and the others had nonspecific changes also, although one did have malignant invasion of the pericardium. One is scheduled for open surgical biopsy, four are under observation and unchanged after periods ranging from six months to one year, one died, and the other has been lost from the study. The patient who died was something of an enigma, a situation which is not uncommon. He was included in the study after tubercle bacilli had been cultured from the pleural fluid. However, he definitely had clinical evidence of severe rheumatic heart disease. The fluid in the right hemithorax was thought to represent a transudate due to the heart failure, and he was therefore classified in the indeterminate group. He was re-admitted and pleural biopsy was performed which demonstrated only nonspecific changes; at postmortem examination three weeks later no evidence of an active tuberculous process was found in either the lung or the pleura, and rheumatic heart disease was obvious. Whether this truly represents tuberculosis is still conjectural.

Of the nine patients in this group from whom inadequate tissue was obtained (table 3), three were subjected to surgical biopsy and nonspecific

pleuritis was demonstrable in all three, with lung biopsy in two giving findings compatible with infarction which was therefore assumed to represent the etiology of the effusion. The other patient had a pseudocyst of the pancreas which was marsupialized, but no obvious lung or pleural disease was discernible. The other six either had contraindications to surgical biopsy or refused the procedure. Postmortem examination was, however, obtained in four, and infarction of the septic variety was demonstrable in two, the third had histologic changes compatible with disseminated lupus, and in the fourth there was only a hydrothorax, with normal pleura and secondary to severe rheumatic heart disease. The remaining two patients are still alive and under observation, with the presumptive diagnosis of multiple septic infarcts in one, and in the other substantial clinical evidence of lupus erythematosus.

In this group of patients, even though pleural tissue was obtained in 12, an etiologic factor was determined with certainty in only two. These were tuberculous, and proper therapy was accordingly instituted. In the others various causes were suggested as precipitating factors. Probably the most significant conclusion to be drawn from this group is that all of these patients could well have been treated as tuberculous since the early clinical courses and, in some, even subsequent courses, were not incompatible with this diagnosis, although admittedly all were not typical. That some, in truth, may still have been due to tuberculosis is a possibility, although unlikely. That more than one represented disseminated lupus is also possible, and the probability that there is an entity of idiopathic benign pleuritis, not too dissimilar to its pericardial counterpart, or that the two are actually the same disease with different manifestations, has theoretic implications of an unexplored nature.

Results in the Surgical Group

This group consisted of those patients in whom aspiration biopsy had not previously been performed (33 cases), and those in whom the histologic results obtained at aspiration biopsy were either inadequate or thought to be inconclusive (21 cases). In most instances the procedure employed was the small intercostal incision, as advocated by Klassen,[12] but in some the removal of a small section of rib, coupled with a complete exploration, was performed. Obviously some required water seal drainage postoperatively, but in general this was not necessary. Two patients had a significant complication—empyema. Both were patients in whom tuberculosis had been found, and, significantly, both had received at least three to four weeks of antituberculosis therapy prior to biopsy. Moderate degrees of residual pneumothorax and air leaks occurred in six other patients in the immediate postoperative period.

As was expected, the most frequent finding was a granulomatous pleuritis (table 5). Not only was this histologic finding the *first* confirmatory evidence obtained, but in most instances it was also the *only* evidence available.

TABLE 5

Results Obtained in the 54 Patients in Whom Surgical Biopsy Was Performed

Indication for Surgical Biopsy	No.	G	NSP	Mal.	Nor.	Inad.
A. Inadequate specimens obtained at aspiration biopsy	7	3	4	0	0	0
B. Nonspecific pleuritis obtained at aspiration	14	5	6	3	0	0
C. No prior biopsy	33	15	11	2	4	1
Totals	54	23	21	5	4	1

The ability to demonstrate tubercle bacilli from sections of the pleura was disappointing, although considerably better than by conventional methods. Gridley and periodic acid Schiff stains were also routinely employed.

The results obtained in the patients from whom inadequate specimens had been taken in the aspiration group are listed in table 3, and present no particular problem. In the other group of aspiration biopsies (that in which nonspecific pleuritis was found), the results of the surgical biopsies have previously been discussed but bear reëmphasis. Fourteen such patients were studied, and in six the finding of nonspecific pleuritis was substantiated; in five others there was evidence of granulomatous pleuritis (figure 4), and

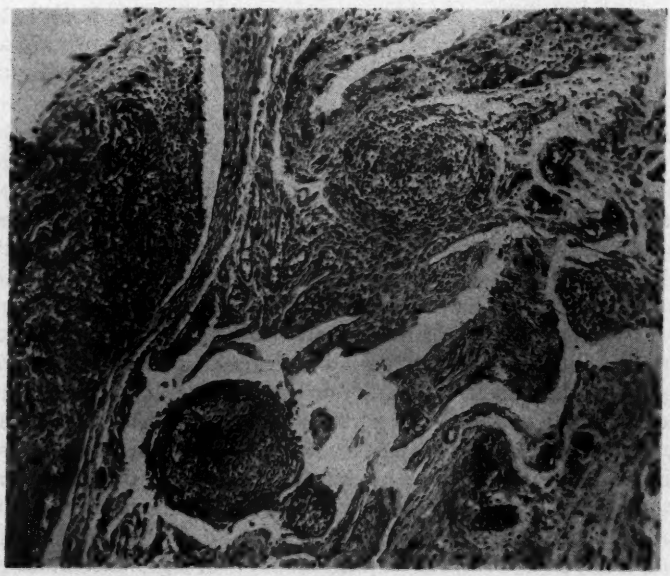

FIG. 4. Histologic section of the pleura obtained at surgical biopsy without exploration, demonstrating noncaseating granuloma. Aspiration biopsy previously had yielded only nonspecific inflammatory changes.

in the remaining three malignancy was demonstrable. These seeming false-negatives obtained by aspiration will be discussed subsequently.

The third group, i.e., those on whom aspiration surgical biopsy had not previously been performed, also proved interesting from several distinct aspects (table 5). First, tuberculosis was again the most common etiology. Second, 11 of the 33 had only nonspecific changes, and therefore were not subjected to long-term antituberculosis treatment. Third, normal pleura was obtained in four patients, one of whom was subsequently proved to have tuberculosis by repeated positive gastric cultures. Actually, therefore, 14 patients in whom the clinical course, skin tests, etc. were compatible with tuberculosis had at pleural biopsy no evidence to incriminate the tubercle bacilli as the etiologic agent. Fourth, two patients in whom surgical biopsy yielded evidence of nonspecific inflammation came to autopsy two and four months later and both had definite evidence of carcinoma involving the pleura. Another patient with nonspecific findings at surgical biopsy also had two gastric cultures positive for tubercle bacilli returned subsequent to the biopsy. In the remaining eight patients no specific cause was ever determined.

It would seem, therefore, that the group of patients with nonspecific changes obtained at surgical biopsy were as interesting and controversial as the same group subjected to aspiration biopsy.

Discussion

The need for additional diagnostic technics to establish rationally an etiology for many cases of pleural effusion is quite apparent on analysis of the high percentage of such patients classified as indeterminate or idiopathic after thorough study.[13, 14, 15] The ability to diagnose such cases is certainly of academic interest, but such ability becomes imperative when experience indicates that an unknown but significant number of such patients are, and have been, improperly classified and treated because of the problem of differential diagnosis. The dilemma is further accentuated when one realizes that the two disease processes which account for a significant percentage of pleural effusions, i.e., malignancy and tuberculosis, not only constitute the major disease entities involved in the differential diagnosis, but also are associated with the highest incidence of increased morbidity and mortality. Even more important are the prognostic, therapeutic and socio-economic implications intimately related to our ability to distinguish between effusions of tuberculous and those of nontuberculous origin. That this problem is significant is readily confirmed by the wealth of contributions to the literature concerning this subject in the last 30 to 40 years.

The knowledge that 65% of patients with "idiopathic" pleurisy with effusion may develop pulmonary and/or extrapulmonary tuberculosis within five years if inadequately treated,[16] and the recent Veterans Administration report [17] of benefits derived from chemotherapy in tuberculous pleurisy with

effusion, have further influenced the eagerness with which the physician institutes appropriate antituberculosis therapy. The same authors who report this high incidence of tuberculosis developing in their admittedly select group of patients further imply that all such patients should receive chemotherapeutic agents, since an analysis of all of the early clinical features of these patients, including the size and location of the fluid, the cytologic characteristics, bacteriologic studies of the aspirated fluid, and even the rapidity with which the x-ray clears, has valuable significance but does not materially aid in establishing diagnosis. For, in truth, the highest incidence of tuberculosis developing in any group without the benefit of chemotherapy (70%) was noted in those in whom the post-treatment x-ray was interpreted as clear or normal. Furthermore, 60% of the patients in whom the examination of the pleural fluid yielded no evidence of tubercle bacilli on culture subsequently relapsed, whereas only 64% of those whose fluid was positive relapsed. (They do, however, suggest that in cases of doubt, or especially if the skin test (PPD) is negative, pleural biopsy is desirable.)

Further confusion occurred, however, when Sutliff,[2] following biopsy of the pleura in 21 cases for diagnostic purposes, concluded that pleural densities which persist for more than two months are probably tuberculous in origin, and that the procedure was of no additional value in the younger age groups. Yet recently Stead and colleagues [4] were able to demonstrate no evidence of tuberculosis at thoracotomy, including lung biopsy, in nine of 24 patients (most of whom were in the younger age group) with prolonged persistent effusions thought to be of tuberculous origin which had been present for an average of 11.3 months. It is therefore obvious that classic clinical pictures are not always decisive, and this further supports the need for proof of an etiology.

If, indeed, biopsy of the pleura is a useful and accurate procedure—which now seems apparent—it remains conjectural in the minds of many as to which type (aspiration or surgical) should be employed, in which cases it is indicated, and at what time in the course of the effusion the procedure should be undertaken.

In a comparison of the value of diagnostic procedures, various factors should be considered. These include ease of performance, and the attendant degree of morbidity and mortality compared with the rapidity and accuracy of the results obtained. We feel that aspiration biopsy is superior to the surgical approach. It can be performed with the same degree of ease as a thoracentesis, it is associated with the same minor complications, and has been accompanied by no increase in morbidity and no mortality in the more than 100 cases reported in the literature. In most instances the histologic results are available within 48 to 72 hours, and in our series aspiration biopsy was usually performed at the time of the first thoracentesis. More experience is required to attest dogmatically to its accuracy, since the complete significance of nonspecific inflammatory changes is unsettled, but it

apparently is as accurate as surgical pleural biopsy when the latter is performed without total surgical exploration.

We therefore feel that aspiration biopsy should be employed in any case where a diagnostic thoracentesis is to be performed, and do not agree with Sutliff that biopsy offers no advantage over conventional methods.

Conversely, for numerous reasons, surgical biopsy cannot be performed in every case of pleural effusion. It is a procedure of some significance, requiring the services of a surgeon and anesthetist and the use of an operating room. When performed early in the course of a tuberculous pleurisy with effusion it is associated with increased morbidity, and when performed late may be associated with both increased morbidity and mortality in those cases of nontuberculous etiology.

The accuracy of surgical biopsy, like that of aspiration biopsy, can also be challenged, especially when the former is performed without total exploration. The finding of nonspecific changes in pleura obtained surgically has the same significance as it does when obtained by aspiration biopsy. We have had "false-negatives" in both groups, and other investigators have reported similar findings. Heller [7] reported a case in whom surgical biopsy yielded only fibrin; subsequently, a caseating granuloma was obtained by aspiration biopsy.

The recommendation of Breckler [3]—that biopsy be performed through the seventh and eighth interspace at the anterolateral aspect—should not be accepted without qualification, since it has resulted in false-negatives in our series. We have previously reported [10] obtaining changes in the pleura of a nonspecific nature in this area, and of granulomatous pleuritis at a higher level contiguous to a subpleural tuberculous focus. Stead and his colleagues [4] also emphasize this point. In two other cases we also have found nonspecific changes at this level, but definite bacterial and clinical evidence to support the diagnosis of tuberculous pleurisy. We would therefore recommend that, if any parenchymal focus is demonstrable either on a conventional posteroanterior chest film or on a tomogram, the biopsy be performed at that level of pleura contiguous to this lesion.

The accuracy of aspiration biopsy has always been questioned by opponents as the outstanding disadvantage in this type of procedure, whether it be utilized in liver, kidney or pleural disease. Fifteen patients in the aspiration group in whom evidence of nonspecific pleuritis was obtained probably were false-negatives, since, in truth, a specific cause was subsequently delineated. However, six of these were documented only at postmortem examination. It is also pertinent that of the nine in whom surgical biopsy uncovered a specific cause, full exploration was required in four.

In the surgical group, false-negatives also were subsequently discovered in five of 33, malignancy in three and tuberculosis in two.

The surgical method, especially when full thoracotomy is employed, is the more accurate (figure 5). However, if one is cognizant of the limita-

tions of aspiration biopsy, and simultaneously appraises the advantages previously mentioned, it remains a highly productive diagnostic procedure and should be employed initially, with reservation of the surgical procedure —with or without total exploration—to those cases that may require it.

FIG. 5. Section of pleura showing malignant involvement. This was a 43 year old Negro male in whom both aspiration biopsy and surgical biopsy without full exploration had yielded pleura without specific changes. Only when full exploration was performed was the malignant nature discovered.

SUMMARY AND CONCLUSIONS

The literature on pleural biopsy has been briefly reviewed, and the advantages of employing this procedure in the study of pleural effusion have been discussed.

The results of 132 pleural biopsies are presented, and the surgical and aspiration methods are compared.

It is concluded that aspiration biopsy is the initial method of choice and should be employed early in the course of the effusion—routinely at the time of the initial thoracentesis.

Surgical biopsy, with or without total exploration, should be reserved for those individuals in whom aspiration biopsy has not proved rewarding.

Both tuberculosis and malignancy may be present and yet the pleura demonstrate only nonspecific changes.

Patients in whom tuberculosis is suspected as the cause of a pleural effusion should not be subjected to long-term chemotherapy, with all its

implications, without either histologic and/or bacteriologic confirmation, which preferably should be obtained early. If this cannot be accomplished utilizing conventional methods, including aspiration biopsy, then surgical biopsy should be undertaken. A frozen section of the pleura should be obtained through an intercostal approach and, if inconclusive, full exploratory thoracotomy is then warranted.

An entity of pleuritis due to an undetermined agent probably exists which, in its clinical manifestations, is not too dissimilar to its pericardial counterpart, idiopathic benign pericarditis.

Summario in Interlingua

Un analyse del resultatos de 132 biopsias del pleura parietal indica que iste relativemente recente technica diagnostic ha distincte avantages in comparation con le methodos que es currentemente in uso. Le combination del nove technica con le methodos acceptate resulta in diagnoses etiologic in un plus alte procentage de casos. Le possibilitate de obtener iste information a bon tempore e de instituer un therapia rational promptemente exerce un influentia super le morbiditate e le mortalitate.

Currentemente, tres methodos de biopsia del pleura parietal es utilisate. Duo de illos es del typo chirurgic e require le servicios de un anesthesiologo. Le differentia inter illos es primarimente que le un se face per un incision intercostal durante que le altere require un partial resection costal. Le tertie methodo utilisa un technica bioptic a aspiration o punceation, simile a illo usate in biopsias hepatic e renal. Le application del tres mentionate methodos a specific situationes clinic es tabulate e analysate. Distincte avantages resulta del uso del typo aspirational de biopsia in omne casos de idiopathic effusion pleural. Le mesme typo provide un rapide manovra diagnostic in effusiones que es obviemente causate per tuberculose o per un crescentia maligne. Si le biopsia aspirational non resulta in un diagnose specific, il es justificate—in le absentia de contraindicationes—effectuar un biopsia intercostal con congelation immediate del section. Si etiam iste manovra detege nulle specific causa histologic, thoracotomia con exploration complete debe esser effectuate.

Super le base de iste principios diagnostic, un agente etiologic pote esser detegite in plus que 90% del casos.

Le experientia ha demonstrate que le biopsia aspirational e etiam le biopsia chirurgic sin exploration pote producer "pseudo-negative" reportos histologic. Es presentate exemplos de casos in que pleuras, que demonstrava al biopsia solmente alterationes de character non-specific, se provava subsequentemente afficite per malignitate o per tuberculose. Le conclusion es que le constatation de non-specific alterationes in le pleura super le base de biopsias aspirational non pote esser considerate como diagnostic e que le tractamento debe esser instituite solmente post que thoracotomia con appropriate biopsias ha essite effectuate.

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THE MEDICAL ASPECTS OF MOTOR VEHICLE ACCIDENT PREVENTION *

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PHYSICIANS are spending a great deal of time and effort in the study of disease in order to prolong life. Yet according to *Accident Facts,* 1957 Edition,[1] the leading cause of deaths for persons of from one to 24 years of age is accidents. Motor vehicle accidents account for 42% of all accidents. In the age group from 25 to 44 years, heart disease is the leading cause of death, with accidents second and cancer third. In the group from 45 years on, heart disease and cancer lead accidents as the cause of death. There were 95,000 deaths due to all accidents in 1956. Forty thousand were due to motor vehicles. There were 1,400,000 injuries as a result of motor vehicle accidents in 1956. In other words, there is a motor vehicle death every 13 minutes and an injury every 23 seconds. Any disease causing such mortality and morbidity deserves much more attention from the medical profession than it has heretofore received. Motor vehicle accidents must be studied in the same way as any other disease.[2]

Organized medicine and some individual physicians are beginning to realize the importance of this public health program.

In 1940 the American Medical Association, aware of the importance of medical factors in safe driving, prepared standards of physical fitness for drivers.[3] Kerr [4] and Dunlop [5] in 1945 reviewed the standards for drivers. Realizing the importance of the driver in accident prevention, the Industrial Medical Association in 1954 appointed a committee to study and establish physical and mental standards for motor vehicle drivers. In 1956 Brandaleone and Friedman [6] published a list of physical standards for vehicle drivers. In 1956 the American Medical Association appointed a Committee on Medical Aspects of Automobile Crash Injuries and Deaths. In 1957 Brandaleone et al.[7] reported their recommendations for medical standards for motor vehicle drivers.

The three major factors involved in motor vehicle accident prevention (figure 1) are the road, the vehicle and the driver. Great strides have been made in the improvement of the road and the vehicle. However, the human element, the major factor in accidents, has been neglected. There are nonmedical and medical factors to be considered in accident prevention. The nonmedical factor consists of safety education and training. The medi-

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cal factors, which are of concern to us, may be divided into three main categories:

1. Organic.
2. Psychologic.
3. Drugs.

It has been reported that one out of every 14 drivers involved in fatal accidents had a physical condition that could have been a contributing factor to the accident.[1a] Lack of sleep and fatigue were present in 60% of the cases, with defective vision, illness and defective hearing next in order.

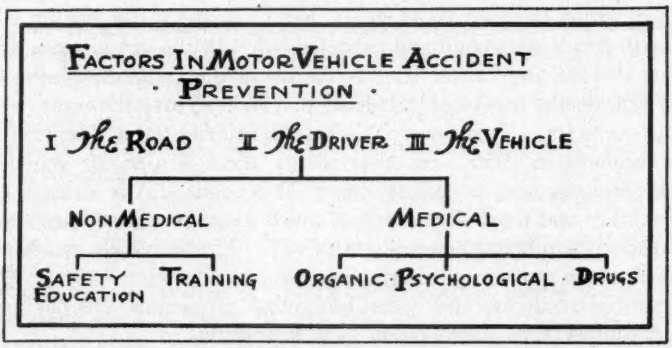

FIG. 1.

In the interest of public safety, the physician must assume his proper role in accident prevention. It is his responsibility to determine the qualifications of a patient, and to advise him when his physical condition militates against safe driving.

The purpose of this paper is:

1. To present the results of a comprehensive medical program on the reduction of motor vehicle accidents.
2. To stimulate the physician to assume his proper role in motor vehicle accident prevention.
3. To stimulate research in the various phases of motor vehicle accident prevention, especially as to the effect of specific medical factors in accident prevention.

METHOD OF STUDY

A comprehensive medical program was established in an industrial organization. The program included careful preplacement and periodic medical examinations and the study of all absences due to illnesses or accidents.

Preplacement Examinations

The institution of an improved driver selection program was one of the important factors in the reduction of accidents. Following the personnel interview and preliminary testing, the applicant was given a complete medical evaluation, including a thorough history, physical examination, urine, complete blood count, sedimentation rate, Wassermann test, chest x-ray and electrocardiogram. The candidate was then classified according to the profile system, the details of which have been previously reported.[8]

Briefly, the profile is based on a system used in World War II by the Air Force. It includes a physical and mental examination and is divided into six categories (figure 2):

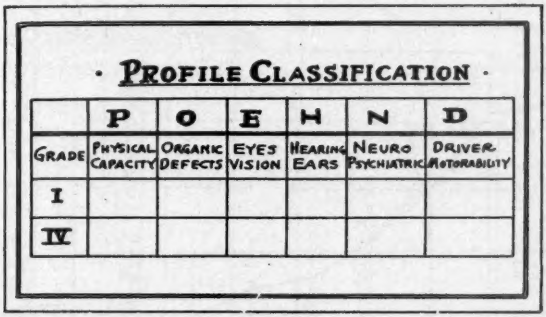

Fig. 2.

Physical, organic, vision (eyes), hearing (ears), neuropsychiatric and driver motorability tests. Each category is subdivided into four classifications, 1 representing the highest and 4 the lowest grade in each category. The grade of 4 in any group disqualifies the candidate.

Briefly, any candidate is rejected who might present a disability that would suddenly incapacitate him and be the direct cause of an accident. However, candidates are also disqualified for conditions that may be indirectly incapacitating. For example, severe hemorrhoids may cause a bus operator so much discomfort that his attention may be diverted and cause him to be involved in an accident. When a candidate is finally accepted he is put through a rigid driver training program by the safety and personnel departments.

In addition to the preplacement examination, whenever an employee was absent for more than 28 days because of illness or injury he was examined to determine his ability to drive safely. These periodic examinations disclosed many illnesses, some temporarily and others permanently disqualifying. When possible, the disabilities were corrected. If an employee was temporarily prevented from driving, an attempt was made to find other work for him.

Results

The comprehensive medical program under study was introduced almost 10 years ago. The accident rate under operator control during this period can be seen in figure 3. In 1946 there were 6,377 accidents. This number was reduced to 3,608 in 1950, to 2,568 in 1953, and to 2,713 in 1956. In an effort to be critical of our results, we compared them with those of similar major transit companies throughout the United States. We obtained data from the American Transit Association concerning six comparable companies, all of whom reported their accidents according to stand-

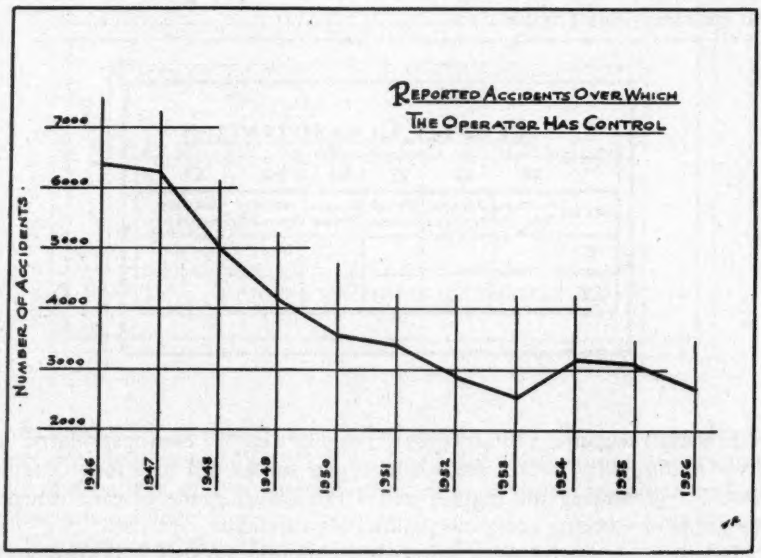

Fig. 3.

ard procedures as established by the American Transit Association. Figure 4 shows the dotted line representing the average rate of the six companies. The solid line represents the accident rate of the company under study.

Study of Accident Repeaters

A study of accident repeaters resulted in some interesting observations (table 1). In 1948 there were 211 operators (out of approximately 2,000) who were habitual accident repeaters, that is, they were involved in three preventable accidents in a six-month period. One hundred fifty-six of these accident repeaters (Group A) were referred for special safety hearings.

These 156 men had 585 accidents, or 3.75 accidents per man, during the six-month period immediately before the study. They were involved in

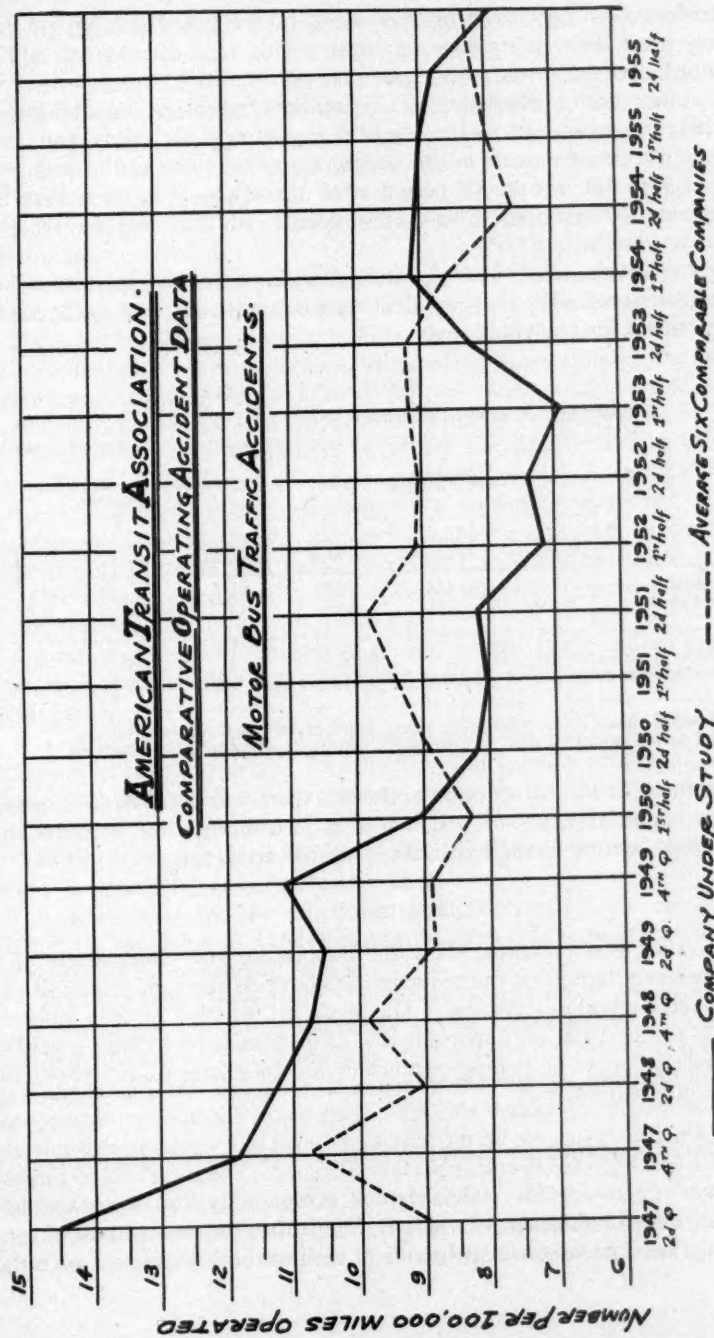
AMERICAN TRANSIT ASSOCIATION.
COMPARATIVE OPERATING ACCIDENT DATA
MOTOR BUS TRAFFIC ACCIDENTS.
NUMBER PER 100,000 MILES OPERATED
15
14
13
12
11
10
9
8
7
6
1947 2d Q
1947 4th Q
1948 2d Q
1948 4th Q
1949 2d Q.
1949 4th Q
1950 1st half
1950 2d half
1951 1st half
1951 2d half
1952 1st half
1952 2d half
1953 1st half
1953 2d half
1954 1st half
1954 2d half
1955 1st half
1955 2d half
COMPANY UNDER STUDY
AVERAGE SIX COMPARABLE COMPANIES
A.T.A IDENTIFICATION NUMBERS 130 · 360 · 422 · 630 · 703 · 704.

FIG. 4.

451 accidents, or 2.90 accidents per man, in the six-month period immediately after their safety investigations. This is a decrease of 22.7% in the number of accidents.

The other group, consisting of 55 accident repeaters, in addition to safety hearings, was sent to the Medical Department for study and care. When their accident records in the six-month period prior to the study are compared with the six-month period after the study, it is seen that the accident rate was reduced from 3.11 accidents per man to 0.51 accident per man, a decrease of 83.6%.

In other words, safety hearings and retraining alone did not accomplish the results achieved when these accident repeaters were also sent to the Medical Department for study and care.

TABLE 1

A Study of 211 Accident Repeaters (3 Accidents in 6 Months)

	Group A Safety Hearings			Group B Medical Examinations and Safety Hearings		
	Number of Repeaters	Number of Accidents	Accidents per Man	Number of Repeaters	Number of Accidents	Accidents per Man
First period	156	585	3.75	55	171	3.11
Second period	156	451	2.90	55	28	0.51
Decrease in accidents per man			0.85			2.60
Decrease in per cent			22.7%			83.6%

First period equals six months *before* safety hearings and medical examinations.
Second period equals six months *after* safety hearings and medical examinations.

In addition to the reduction in accidents, there was a substantial saving due to decreased absenteeism, and reduction in compensation accidents and liability costs because of the reduction in vehicle accidents.

DISCUSSION

The results just presented show the importance and effectiveness of a comprehensive program on the reduction of accidents through proper driver selection and medical observation. The physician, whether he is in industry or private practice, has an important role to perform in certifying a patient for a driver's license or issuing certificates for Interstate Commerce Commission examinations.

MEDICAL FACTORS IN MOTOR VEHICLE ACCIDENT PREVENTION

Organic Factors: Our standards for acceptability for motor vehicle drivers have been published elsewhere.[6] We realize the present lack of concrete statistical data concerning the role of each medical defect as a potential

driving hazard. However, because of the present high mortality and morbidity of motor vehicle accidents, we must not delay until the results of properly controlled studies are obtained. We feel that a medical opinion based on our knowledge of physiology and clinical medicine can be formulated as to the potential danger of various pathologic states. All drivers should pass the minimal visual and auditory requirements. There seems to be no question that a person suffering with a disease that might suddenly incapacitate him should not be permitted to drive unless his condition has been under control.

For example, a diabetic on insulin who has frequent insulin reactions, or a patient with uncontrolled convulsive seizures, should not be permitted to drive. Certain neurologic conditions that might be incapacitating should be disqualifying. Aortic stenosis, congestive heart failure, carotid sinus syndrome, Adams-Stokes syndrome, or any other cardiac condition that might suddenly incapacitate the driver, should be disqualifying.

A candidate with tuberculosis or severe low back syndrome should not be qualified for the job of driving a commercial vehicle or truck if he is required to do heavy lifting. In industry a thorough knowledge of the job requirement is necessary in order to evaluate the candidate properly. Our experience has shown that usually 35% of the candidates fail to qualify.

Drug Factors: Alcohol is known to be the most important drug factor in accident causation.

Antihistamines and tranquilizing drugs which might induce drowsiness must be prescribed with a great deal of caution to persons who drive motor vehicles.

It has been shown that some antihistamines are almost as potent as barbiturates in inducing sleep. As a matter of fact, many proprietary preparations sold for their sleep-producing effect are essentially antihistamine preparations.

Antihypertensive drugs carry a potential danger for two reasons: (1) sedative effect, and (2) hypotensive effect.

Amphetamine and the other stimulating derivatives are not dangerous per se, but are dangerous only because the driver depends on the medication to overcome overwhelming fatigue.

The Interstate Commerce Commission records reveal a case of a driver who had been using amphetamine for enforced stimulation. He had fallen asleep at the wheel, driven his large trailer truck off the road into a river bed and been killed. A letter addressed to his brother, found on the driver's body at the time of the investigation into his death, stated that he had been driving continuously for three days without sleep, using "Benny" (Benzedrine) to stay awake. Like so many others, this driver expected Benzedrine to do more than it is capable of doing.

Psychologic Factors: The majority of motor vehicle accidents are probably due to psychologic factors. Our experience has been that an operator

who passed a group of psychologic tests had an accident record statistically significantly better than that of a candidate who did not pass the tests.[9] It is our opinion that the future development of a program of motor vehicle accident prevention will depend on the better understanding of the psychologic problems involved. It has been impossible as yet, to determine the exact nature of these psychologic changes. Some people suffer acute episodes of stress and, as a result, drive recklessly. I am sure that all of us have gone through tense emotional periods when we were late for our hospital clinics, or late to see a seriously ill patient, and have driven more recklessly than usual.

The chronically unstable individual is a great public safety hazard. The following case may demonstrate the effect of emotional instability.

A 28 year old white male driver was severely disturbed over his five year old, mentally retarded child who was a patient in a state hospital. The doctors had just informed him that the prognosis was extremely poor. He came to the medical department for advice, and was found to be so depressed that he was advised to discontinue driving. The only position available at the time was that of a cleaner in a garage. In an effort to assist him and not increase his difficulties, he was permitted to accept this job. He continued to be disturbed about his child, and one day while driving in a garage he pinned an employee against another vehicle and killed him.

Research

The need is great! Research is essential! Although minimal physical and mental standards for licensing drivers have been suggested, confirmation of their validity is desirable. Screening tests must be devised.

Funds for such essential research will probably be available through the Accident Prevention Bureau of the United States Public Health Service, sponsored by the National Institutes of Health.

You, as physicians, and particularly as specialists, have the following functions to perform in order to prevent motor vehicle accidents:

1. To establish medical standards for licensing drivers of various categories, civilian, commercial vehicle and transportation.
2. To determine the type and frequency of necessary periodic examinations.
3. To engage in research concerning the relationship of specific organic and psychologic states to motor vehicle accidents.

Summary

1. The results of a comprehensive medical program on motor vehicle accident reduction are presented.

2. The organic, psychologic and drug factors in motor vehicle accident prevention are discussed.

3. The importance of the physician in evaluating the physical qualifications of vehicle operators is emphasized.

4. The need for research to determine the relationship of specific organic disabilities and psychologic states to accident causation is stressed.

Summario in Interlingua

Le crescente numero de mortes e de serie vulnerationes occurrente in consequentia de accidentes de vehiculos a motor face del prevention de tal accidentes un importante problema de sanitate public. On ha estimate que 40.000 mortes e 1.400.000 vulnerationes per anno costa plus que quatro milliardos dollars.

Le importantia del medico in le question del reduction de accidentes de vehiculos a motor esseva demonstrate per le resultatos de un comprehensive programma medical que consisteva de:

1. Un detaliate examine pre-ingagiamental como parte de un meliorate programma de selection de chauffeurs.
2. Periodic examines medical.
3. Un studio de omne absentias causate per maladias e accidentes.
4. Appropriate placiamento del obreros.

Iste programma resultava in un reduction del numero de accidentes ab 6.377 in 1946 a 2.568 in 1953 e a 2.713 in 1956.

Omne le examines esseva classificate secundo un "systema profilate."

Le factores de signification in le prevention de accidentes de vehiculos a motor es (1) le strata, (2) le vehiculo, e (3) le chauffeur. Le presente reporto es concernite con le rolo del chauffeur. Le factores medical es classificabile in le major categorias de (1) organic, (2) psychologic, e (3) drogal. Iste tres categorias es discutite.

Le medico debe esser conscie de su importantia in determinar le qualificationes del chauffeurs.

Existe le urgente desiderato de recercas additional pro determinar le relation inter condition physic e factores psychologic de un latere e le prevention de accidentes del altere.

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AGRANULOCYTOSIS ASSOCIATED WITH PROMAZINE ADMINISTRATION: REPORT OF THREE CASES *

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CHLORPROMAZINE has been widely administered for several years. Two of the most serious complications reported from its use are jaundice and agranulocytosis. Forty-five cases of the latter were collected in a report in 1956,[1] and several more have been added since, with an estimated incidence of less than 0.3%. Other reviews of this problem have appeared recently in the literature.[2, 3]

Promazine † has been increasingly popular since the early favorable reports of its use in May, 1956.[4, 5] It differs structurally from chlorpromazine only in the absence of a chloride radical in the 2-position of the phenothiazine ring. Reports of complications associated with promazine have only recently begun to appear. Two cases of agranulocytosis have been published to date.[6, 7]

Three additional cases of agranulocytosis developing during therapy with promazine are presented in this paper (table 1).

CASE REPORTS

Case 1. A 73 year old white female with known pernicious anemia of 30 years' duration, well controlled with regular injections of refined liver extract and vitamin B_{12}, was first admitted to Strong Memorial Hospital in October, 1956, because of a fractured left ankle. During this hospitalization she received a single 25 mg. dose of chlorpromazine.

She was readmitted on March 18, 1957, because of chronic alcoholism, with malnutrition, peripheral neuropathy and mental agitation. She was given a high protein diet, multivitamins and paraldehyde, and improved steadily. Two single 200 mg. doses of promazine were administered intramuscularly on March 18, 1957. On March 22, 1957, oral administration of promazine was started, 150 mg. per day. A hemogram on March 18, 1957, showed a hematocrit of 43% and a white cell count of 4,300 per cubic millimeter, with a normal differential count. Serum icterus index was 10. The patient was discharged to her home after 21 days on April 8, 1957, with medications which included promazine, 150 mg. per day, monthly injections of 50 μg of vitamin B_{12}, and multivitamins. She also took phenobarbital occasionally, and continued the weekly liver extract injections which she had obtained previously from another physician.

The patient returned to the emergency department on May 2, 1957, complaining

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of fatigue, mild diarrhea, dysuria, and hesitancy of four days' duration. Two days before admission she had developed fever, chilliness, a dry cough, a slight sore throat and increased weakness. The diarrhea subsided on the day of admission.

Physical examination revealed a blood pressure of 110/60 mm. Hg, a pulse rate of 120 per minute, respirations of 18 per minute, and an oral temperature of 40.2° C. The patient was acutely ill, tremulous, flushed and lethargic, and had a dry cough. Pharyngeal and nasal mucosa were reddened and edematous, with mucopurulent exudate. Diffuse cervical adenopathy and dullness and crackling râles at the right lung base were noted. Sinus tachycardia was present, with a harsh precordial systolic murmur. Neurologic examination revealed generalized hyporeflexia, normal plantar responses, and absent vibratory sensation in the lower extremities. The remainder of the physical examination was unremarkable.

TABLE 1

Summary of Three Cases

	M. W., 73, Female	N. I., 74, Female	J. B., 58, Male
Indication for treatment:	Agitation, chronic alcoholism	Agitation, chronic asthma	Intractable angina pectoris
Other known diseases:	Pernicious anemia, peripheral neuropathy	Bronchitis, emphysema, general arteriosclerosis	Arteriosclerotic heart disease
Promazine, time and dosage:	6.5 gm. in 42 days	11.7 gm. intermittently for 6 months, steadily for 2 months	2.75 gm. in 31 days
Presenting symptoms:	Fever, diarrhea, cough, sore throat-4 days	Fever, diarrhea, cough, sore throat-4 days	Fever, cough, sore throat-2 days
Lowest white cell count:	250 per cu. mm.	Less than 200	900
First neutrophils:	3rd day	—	4th day
Further course:	Afebrile by 10th day	Continued fever, monilial infection	Afebrile by 4th day
Drugs used:	Penicillin, streptomycin, tetracycline, nystatin, probenecid	Penicillin, tetracycline, prednisone, nystatin	Penicillin, streptomycin, dihydrostreptomycin
Outcome:	Discharged, recovered, on 28th hospital day	Died on 6th hospital day	Discharged on 14th hospital day; died 4 months later

Laboratory data on admission revealed a white cell count of 250 per cubic millimeter, with only lymphocytes and a few monocytes seen on peripheral blood smear. Platelets were normal. Hemoglobin was 13.6 gm.%; hematocrit, 41%; corrected sedimentation rate, 32 mm. per hour (Wintrobe). Urinalysis showed 3 plus albuminuria, and the spun sediment contained one to three white cells and occasional red cells per high power field. *Streptococcus viridans* grew on culture of the urine. Stool culture and examination and blood culture were negative. Nose and throat culture revealed *Staphylococcus aureus hemolyticus* and *Klebsiella pneumoniae*. Sputum culture grew out the former organism only. Blood chemical tests showed: sodium, 127 mEq./L.; potassium, 3.0 mEq./L.; icterus index, 16; serum total bilirubin, 2.8 mg.%, with a direct bilirubin of 0.1 mg.% and an indirect bilirubin of 2.7 mg.%; cephalin flocculation, 3 plus in 24 hours; serum glutamic oxalo-acetic transaminase, 51 units. Other blood chemical findings and chest x-ray were normal. A bone marrow examination on May 3, 1957, showed erythroid hyperplasia and a maturation arrest at the promyelocyte stage of the granulocytic series.

Band neutrophils first appeared in the peripheral blood smear on the third hos-

pital day, when the total white cell count was 1,800 per cubic millimeter. The count steadily increased to 17,700 per cubic millimeter on the eighth hospital day, then returned to normal levels. The peripheral smear differential showed progressively increasing maturity of the neutrophilic series, becoming normal by the sixteenth hospital day. A marked eosinophilia was first observed on the eighteenth day, rising to 33% by the twenty-first hospital day and falling to 19% on the day before discharge. Subsequent urinalyses and blood chemistries, except for a 4 plus cephalin flocculation, were within normal limits.

The patient was treated with aqueous penicillin, 1,000,000 units intravenously, followed by 600,000 units intramuscularly every four hours, and streptomycin, 1 gm. twice daily. Promazine was discontinued. After two days the streptomycin was stopped and tetracycline, 200 mg. intramuscularly every six hours for six days, nystatin suspension, 2,000,000 units daily for 11 days, and probenecid, 2 gm. daily for eight days, were given. Procaine penicillin was substituted for the aqueous form after 10 days, and all antibiotics were discontinued by the sixteenth hospital day.

The patient's temperature remained around 39° C. for four days, then the fever slowly subsided, and she remained afebrile after the tenth hospital day. Her symptoms slowly but progressively resolved. She was discharged to a nursing home on the twenty-eighth hospital day, asymptomatic except for her chronic peripheral neuropathy.

Attempts to demonstrate leuko-agglutinins in the patient's acute phase serum were carried out by one of the authors (D. A.), using the method of Dausset, Nenna and Brecy.[8] No leuko-agglutinins to white cells of a compatible donor or to the patient's own convalescent white cells, with and without the addition of promazine, could be demonstrated.

Comment: This patient received a total dose of 6.5 gm. of promazine over a 42-day period. No other medications described as associated with agranulocytosis were taken, and her leukocyte response was prompt upon withdrawal of the promazine. The marked eosinophilia developing during the recovery phase is unexplained, and we have been unable to find any previous report of this in such cases. It may be evidence in support of a hypersensitivity mechanism, or may possibly be an unusual recovery response of this patient's marrow to insult. Mild jaundice, such as occurred here, has been described in agranulocytosis due to various causes.

Case 2. A 74 year old white female was admitted to Strong Memorial Hospital for the seventh time on March 21, 1957, with a chief complaint of "fever for two days."

She had been a known chronic asthmatic for over 25 years, and had in the past received many courses of antiasthmatic, antibiotic and adrenal corticosteroid therapy. On May 17, 1957, she developed crampy, nonbloody diarrhea, followed the next day by sore throat, muscle aching and a temperature elevation to 101° F., and two days later by shortness of breath and a hacking cough.

On previous admissions, diagnoses had included syphilis with apparently adequate treatment in 1930, acute viral hepatitis in 1936, bronchial asthma, bronchitis, emphysema and generalized arteriosclerosis. She was known to have allergic skin reactions to iodides, barbiturates and possibly to opiates.

Review of her past record reveals that she had received chlorpromazine, 20 mg. per day for five days in May, 1956, promazine, 100 mg. per day for 13 days, in September, 1956, and again at the same dose level for 14 days in December, 1956. Her family physician subsequently started her on promazine on January 22, 1957, and

she continued to take this, at a dose of 150 mg. per day, for two months. Her total estimated oral intake of promazine thus comes to 11.7 gm. For four weeks prior to admission she had also taken Doriden (glutethimide, CIBA), 250 mg. once a day.

Physical examination on admission showed an obese female who was moderately dyspneic and orthopneic, with a hacking, nonproductive cough. Blood pressure was 160/70 mm. Hg; pulse, 120 and regular; respirations, 36 per minute; temperature, 40.3° C. rectally. Pertinent findings included dryness of skin and mucous membranes, a red, cracked tongue, a diffusely reddened pharynx without membrane or exudate, a few sticky râles at the left lung base, and cardiomegaly with a precordial grade 2 blowing systolic murmur.

Laboratory studies on March 21, 1957, showed a hematocrit of 38%, hemoglobin of 11.9 gm.%, and a white blood count of less than 200 cells per cubic millimeter. No granulocytes were seen. A voided urine was clear yellow in color, with a specific gravity of 1.015 and without sugar, albumin or acetone. Microscopic examination showed three to five red cells and one to two white cells per high power field. During the next five days the hematocrit remained at the same level, and the white count ranged between 350 and 550 cells per cubic millimeter. A blood urea nitrogen on admission was 15 mg.%, but the serum urea nitrogen rose to 90 mg.% four days later. All blood chemical studies gave results within normal limits except for a cephalin flocculation of 3 plus. Nose and throat cultures grew out *Streptococcus hemolyticus*. C-reactive protein was 3 plus.

A sternal bone marrow aspirated on March 22, 1957, revealed total absence of recognizable myeloid elements. The erythroid series showed normal morphology but a substantial degree of hypoplasia. There was a moderate increase in mature plasma cells.

The patient ran a temperature ranging between 39 and 40° C. throughout her hospital stay. She was started on penicillin, 1.2 million units per day, on March 21, 1957, in conjunction with conservative antiasthmatic therapy and fluid replacement. On March 22, at 4:30 a.m., she was inadvertently given a single intramuscular injection of promazine, 50 mg. On March 23, 1957, tetracycline, 1.0 gm. per day, was added to the regimen, as well as prednisone, 20 mg. per day. The patient failed to respond to this therapy. On March 26, 1957, it was noted that the entire oral cavity and posterior pharynx were overgrown by a whitish membrane. Budding yeasts were noted on smear, and cultures of the throat and stool subsequently grew out *Candida albicans*. Treatment was started with nystatin ointment to the mouth and throat, and with 1,000,000 units of nystatin orally every six hours, but the patient died quietly on the evening of March 26, 1957.

An autopsy was performed, and final anatomic diagnoses included: agranulocytosis of the bone marrow, acute and chronic bronchitis, bronchopneumonia, generalized arteriosclerosis, cardiac hypertrophy, and postnecrotic diffuse hepatic fibrosis.

Comment: This lady, with known allergic tendencies, took promazine intermittently for a seven month period. In addition, she also took a small daily dose of glutethimide (Doriden) for a month. To the best of our knowledge, no hemotoxic reactions to the latter drug have been reported at the dosage levels used here. Her bone marrow examination was striking for the total absence of all myeloid elements. The immediate cause of her death was a sudden generalized monilial infection occurring after several days of therapy with penicillin, broad spectrum antibiotics and prednisone. This fungus infection failed to respond to therapy with nystatin, started about eight hours before her death.

Case 3. A 58 year old white male with arteriosclerotic heart disease and a history of two previous myocardial infarctions was first admitted to Strong Memorial Hospital on July 22, 1956. Because of intractable angina pectoris, he received 20 mc. of I^{131} on August 3, 1956. He had previously been receiving Peritrate and Digoxin, which were continued. For sedation he was placed on promazine, 100 mg. daily in divided doses, on July 26, 1956, and he was continued on these medications after discharge to his home on August 6, 1956.

Shortly after receiving the I^{131} he developed a mild sore throat, followed some days later by a low grade fever and some ear pain. His cardiac status seemed to improve. He had only minimal chest pain, but developed intermittent nausea and vomiting two and one-half weeks after discharge. The promazine had been decreased to 50 mg. daily on August 16, 1956, and was discontinued on August 23, 1956. Because of the patient's continued vomiting, Digoxin was stopped on August 27, 1956, and he received two 100 mg. chlorpromazine suppositories, and then was started again on promazine orally, 100 mg. daily.

On August 29, 1956, he noticed increased fever and sore throat, left ear pain and a productive cough, and was re-admitted to Strong Memorial Hospital on August 30, 1956.

Physical examination revealed a blood pressure of 86/56 mm. Hg; pulse, 118 per minute; respiratory rate, 28 per minute; temperature, 40.3° C. The patient was cachectic and appeared to be chronically but only mildly acutely ill. Pharynx and nasal mucosa showed nonexudative inflammation. A dry cough and a few crackling râles in the left scapular area were noted, and moderate cardiomegaly was present. The remainder of the physical examination was unremarkable.

Laboratory data showed a white blood count on admission of 1,400 per cubic millimeter; hemoglobin, 13.4 gm.%; hematocrit, 42%; sedimentation rate, 33 mm./hr. (Wintrobe). Urine and stool examinations and cultures of sputum, nose, throat and blood were negative. Blood chemistries were essentially within normal limits. On August 31, 1956, the white cell count was 900 per cubic millimeter. White cells on the peripheral smears were entirely lymphocytes, and platelets were diminished. Hematologic interpretation on September 1, 1956, was "peripheral agranulocytosis with myeloid hypoplasia and arrest at the promyelocyte stage in the bone marrow."

The patient was treated with procaine penicillin, 600,000 units every 12 hours, and streptomycin, 0.5 gm., plus dihydrostreptomycin, 0.5 gm. daily, and promazine was discontinued on admission. He remained febrile until the fourth hospital day. Digoxin was started again on September 2, 1956, with only slight nausea and vomiting the next day. The patient improved steadily. Granulocytes were first noted in the peripheral blood smear on the fourth hospital day, with a total white cell count of 5,350 white cells per cubic millimeter by the thirteenth hospital day. Antibiotics were discontinued after 13 days, and the patient discharged to his home on the fourteenth hospital day.

Following discharge the patient did well for a period of several months but four months after discharge began going downhill. Because of hoarseness and hemoptysis he was re-admitted for direct laryngoscopy. Three hours after the procedure he was found dead. Autopsy permission was denied.

Comment: This patient received 2.75 gm. of promazine over a 31-day period, with 0.2 gm. of chlorpromazine given just prior to onset of the symptoms leading to the second admission. It is felt that promazine was the principal offender here, and it is of interest that this patient received a smaller total dose and a shorter period of exposure than has been demonstrated in any other case. It is possible that the chlorpromazine given had an additive

effect. On the basis of previous reports, it is not likely that this small dose alone was responsible for the agranulocytosis.

This patient received 20 mc. of I^{131}. In very high doses of I^{131} (100 to 150 mc.), leukopenia has been observed. However, I^{131} does not concentrate in bone marrow to any significant degree, and Myant [9] states that a dosage of 20 mc. of I^{131} is well below that likely to cause any acute radiation damage. The effect on the bone marrow here can in all likelihood be discounted.

Discussion

Table 2 summarizes pertinent data on previously reported and present cases. In all of these the drug was administered for a period of more than four weeks; in all but one patient (J. B.), large total dosages were used. In the two fatal cases it is of interest that bone marrow examinations demonstrated complete absence of myeloid elements in one, and only the presence of myeloblasts in the other.

Prolonged administration and high dosage have been a factor in all previously reported cases of agranulocytosis associated with various phenothiazine derivatives. This has been reported with chlorpromazine [2, 8] and with the recently introduced drug Pacatal.[10]

Table 2

Cases of Promazine Agranulocytosis

Author	Age	Sex	Duration of Rx (days)	Total gm. Promazine	Lowest WBC Count	Bone Marrow	Rx	Result
Woodward and Solomon[6]	57	F	48	33.2	125	Maturation arrest at myeloblast stage	Penicillin, tetracycline, steroids	Died
Chirico et al.[7]	46	F	40	19.5	750	Maturation arrest at promyelocyte stage	Penicillin, tetracycline, steroids	Rec.
Present case, M. W.	73	F	42	6.5	250	Maturation arrest at promyelocyte stage	Penicillin, streptomycin, tetracycline, nystatin probenecid	Rec.
Present case, N. I.	74	F	58 (prior to onset) 13 (6 mo. before) 14 (3 mo. before)	11.7	200	Absence of myeloid elements	Penicillin, tetracycline, prednisone, nystatin	Died
Present case, J. B.	58	M	31	2.75	900	Maturation arrest at promyelocyte stage	Penicillin, streptomycin, dihydrostreptomycin	Rec.

Possible etiologic mechanisms may be of the immunoallergic variety, or may encompass a direct toxic effect on the marrow. Kracke and Parker [11] in 1934 stressed the importance of a "benzamine group," a combination of benzene ring with N, NH or NH_2 groups, in many of the drugs. This has recently been reëmphasized by Dameshek.[12] Promazine possesses such a linkage.

Inability to demonstrate leuko-agglutinins may speak against an immune mechanism. The consistent pattern of prolonged exposure and high dosage is possible evidence supporting a toxic mode of action.

Treatment in all cases reported has included penicillin as well as broad-spectrum antibiotics. Enough data are not yet available to evaluate the usefulness of steroid therapy. In the small series reported here, the two patients receiving steroid therapy died, one of acute pulmonary edema [6] and one of moniliasis (case 2). This latter complication has not to our knowledge been previously reported.

While the incidence of agranulocytosis is quite low, we feel strongly that every physician using these drugs should be cognizant of this possible complication. During long term therapy, periodic white counts should be done, and the patient should be instructed to report early to his physician in case of fever or sore throat. The possible occurrence of fungus overgrowth during antibiotic therapy of agranulocytosis should be watched for.

Summary

Three cases of agranulocytosis associated with promazine therapy are presented. One died from overwhelming monilial infection.

A brief summary of two previously reported cases is given.

Possible etiologic mechanisms and treatment of this condition are discussed.

Summario in Interlingua

Durante que agranulocytosis e etiam jalnessa ha essite reportate non infrequentemente como effecto del administration de chlorpromazina, un revista del litteratura revela solmente duo previe reportos de iste complication occurrente in association con le uso de promazina que es un droga structuralmente affin. Le presente reporto describe tres casos additional de iste genere.

Le prime caso occurreva in un feminina de 73 annos de etate, con confirmate anemia perniciose, alcoholismo chronic, e neuropathia peripheric, qui habeva recipite 6,5 g de promazina in le curso de 42 dies. Le secunde caso occurreva in un feminina de 74 annos de etate, con chronic asthma, bronchitis, e emphysema, qui habeva recipite 11,7 g de promazina intermittentemente durante un periodo de sex menses e continuemente durante un periodo de duo menses. Le tertie caso occurreva in un masculo de 58 annos de etate, con intractabile angina de pectore, qui habeva recipite 2,75 g de promazina in le curso de 31 dies (insimul con micre quantitates de chlorpromazina). Le symptomas de presentation, notate durante periodos de inter duo e quatro dies ante le hospitalisation, includeva febre, tusse, e mal de gurgite in omne tres e diarrhea in duo del patientes. Le minimos del numeration leucocytic variava inter 200 e 900 per mm^3. Le examine de aspiratos de medulla ossee revelava arresto de maturation in le

stadio promyeloide in casos I e III e le absentia total de omne elementos myeloide in caso II. Le therapia usate includeva le administration de penicillina in omne casos, streptomycina o dihydrostreptomycina in duo, antibioticos a large spectros in duo, Nystatina in duo, e prednisona in un. Un patiente (caso II) moriva in consequentia de un fulminante infection monilial que occurreva durante le tractamento con antibioticos e prednisona. Le altere duo effectuava un restablimento hematologic sin incidente.

Nos non succedeva, in un essayo, a demonstrar leuco-agglutininas in le sero. Durante que il es ben possibile que un factor immuno-allergic es de signification etiologic, il es a notar que un exposition prolongate e alte dosages es uniformemente presente in casos de agranulocytosis associate con derivatos de phenothiazina. Isto suggere un possibile influentia toxic super le medulla ossee.

Durante que le incidentia de agranulocytosis es basse, le clinicos es urgite a prestar attention al possibilitate de su occurrentia, specialmente in casos de cursos prolongate de promazina. Le possibilitate del occurrentia de excessive crescentias fungal durante le therapia antibiotic pro agranulocytosis non debe esser oblidate.

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CASE REPORTS

MYOGLOBINURIA AFTER SPONTANEOUS AND INDUCED FEVER: REPORT OF A CASE *

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MYOGLOBINURIA in man, known to be a consequence of trauma to striated muscle, has occurred also in a number of ill defined clinical circumstances. All of the latter have involved striated muscle, although without clear-cut injury. Sometimes severe muscular exercise alone has been the background; in other cases, true muscular disease, of unknown etiology, has been present. The last group consists of "Haff disease," a geographically localized, epidemic, acute affliction of muscle and idiopathic paroxysmal myoglobinuria, with or without interval muscle weakness and atrophy.

The traumas to striated muscle that have resulted in myoglobinuria include crushing injuries,[1] arterial occlusion with subsequent ischemia [2] and high voltage electric shock,[3] all causing severe muscle necrosis. Haff disease has been reported in small epidemics, first in a village bordering on a portion of the Baltic Sea near Konigsberg, Germany,[4] and later on the borders of a small lake in Sweden.[5] The disease in both areas has been characterized by the acute onset of pain, stiffness and tenderness of muscle. Complete recovery has ensued in a few days, without residual weakness. Myoglobinuria has usually been present.[6] A few patients have had multiple attacks. In almost all cases a history of ingestion of fish has been obtained. Individual predisposition has also been considered a factor; however, the cause of the disease is still unknown.

The remainder of reported cases of idiopathic paroxysmal myoglobinuria number 28 at the time of this writing.[7-30] Approximately 18 have been proved spectrophotometrically; the remainder are accepted on the basis of consistent clinical, pathologic or laboratory features. The cases present considerable clinical variability and are probably of differing etiologies. Because of this, attempts have been made to classify them into different groups. Two cases,[8, 9] associated with a more prolonged course and swelling of the limbs, have been thought to represent variants of dermatomyositis. In several other cases, chronic disease resembling muscular dystrophy has been present,[7, 15, 18, 19, 29, 30] either in the patients or in members of their family. A relationship between myoglobinuria and muscular dystrophy has been proposed.[15] On the other hand, pathologic studies have suggested that the chronic muscle changes in myoglobinuria are due to continued subclinical myonecrosis, differing anatomically from muscular dys-

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trophy.[30] The majority of all cases have been characterized by acute episodes of myoglobinuria, sometimes precipitated by exercise, with [28] or without [10, 12, 14, 15, 18, 24, 29] associated exposure to cold. In some, the exercise has had to be performed on an empty stomach; [17] in others, the severe exertion of a convulsion has preceded the acute attack.[25, 30]

Ono,[31] using a serologic method for detecting myoglobin, has reported that myoglobinuria almost always occurs after strenuous exertion or convulsions. However, in only two of the 68 patients studied by him was reddish discoloration of the urine noted. Red to mahogany colored urine has been the hallmark of myoglobinuria in all hitherto reported instances. Its rarity in Ono's series suggests that his method detected quantities of myoglobin much below that usually found in paroxysmal myoglobinuria, and possibly undetectable by the spectrophotometer.

Febrile infectious diseases have sometimes preceded acute paroxysms of myoglobinuria,[14, 26] most strikingly in the case of Bywaters and Dible.[14] Fever has sometimes accompanied the acute attack. However, fever has never been suggested as a precipitating factor in paroxysmal myoglobinuria. In the following case report, fever on several occasions apparently precipitated myoglobinuria.

Case Report

A twenty-two year old white male was admitted to the hospital for evaluation of dark urine in December, 1955.

The patient had developed a sore throat and fever five days prior to admission. Two days later he noted a "tight feeling" in the lumbar region and began to void dark red urine.

In 1953, during basic training for the Air Force, he had experienced a similar progression of sore throat with fever, followed in two days by low backache and the passage of dark red urine, which continued for three days before he was hospitalized. Albumin with red and white blood cells was present in the urine in large quantities for three days after hospitalization. The blood pressure and other vital signs were normal. The urine was sterile; cystoscopy and intravenous and retrograde pyelography were normal. An alpha streptococcus was cultured from his throat. He was treated with penicillin and discharged from the hospital after 13 days. He then completed his training, which involved considerable marching and strenuous calisthenics, without incident.

During 1954 he had several sore throats without fever. The urine never changed color after these episodes. In October, 1955, while being processed to go overseas, he received several routine immunizations simultaneously. He became mildly febrile later that day; the next day the lumbar aching and dark urine recurred. Both ceased after one day and he did not seek medical attention.

The past history was otherwise almost completely noncontributory. He had had occasional fevers as a child and an adolescent. None was followed by red urine. There was no personal or family history of muscular, neurologic or renal disease. In 1949 and 1951, after walking in a woods, he had developed dermatitis and swelling of his hands and face. The attack in 1951 consisted of a severe generalized weeping eruption which slowly cleared; the earlier episode was mild. These were considered to be due to "poison oak."

The patient was first seen in an outlying tactical hospital. The blood pressure was 140/80 mm. of Hg; pulse, 80; temperature, 99° F. The tonsils were enlarged and red. There was mild costovertebral angle tenderness. The urine was dark brown, with a pH of 5.5 and a specific gravity of 1.019. The red cells were too

numerous to count in a high power field after centrifugation. A few white cells and granular casts were present. The albumin test was three plus. There was slight leukopenia; 51% of the white blood cells were mature lymphocytes, 42% were polymorphonuclear leukocytes, 5% monocytes and 3% eosinophils. The red cell count was 5.04 million per cubic millimeter. The patient was treated with penicillin and oral fluids for three days and was then transferred to the base hospital for further evaluation.

Upon arrival he was afebrile; the blood pressure on several determinations was normal. Physical findings were unchanged from the previous examination except for disappearance of the pharyngitis. The urine two days after admission contained

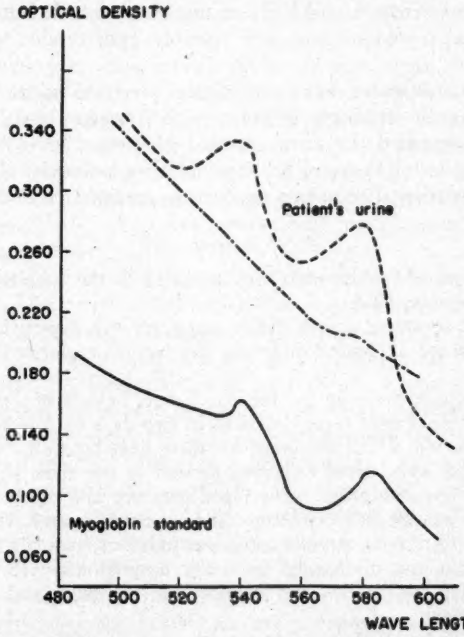

FIG. 1. Spectrophotometric analysis of two specimens of the patient's alkaline urine voided 14 hours postoperatively (herniorrhaphy). Both were grossly discolored, though the quantity of myoglobin differed in the two specimens. A myoglobin standard (oxymyoglobin) is included for comparison.

only a few red cells and no albumin. Thereafter, small amounts of albumin and a few formed elements were inconstantly present. The sedimentation rate (Wintrobe) was 10 mm. per hour.

Because the history strongly suggested a relationship between fever and the urinary abnormalities, approximately three weeks after admission 0.5 ml. of diluted triple typhoid vaccine (calculated as 25 million organisms) was injected intravenously into the patient. Four hours later he noticed lumbar aching. The temperature rose to 102° F. Approximately nine hours after the injection he began to void red to dark brown urine of 6.1 pH. The urine contained albumin (3 plus) and considerable amorphous sediment but only an occasional red cell. It gave a strong positive reaction with benzidine, but contained no bile and only a minimal amount of

urobilinogen. The sediment contained no hemosiderin granules. The plasma hemoglobin was 9.6 mg. per 100 c.c.

Spectrophotometric analysis of the urine indicated that the abnormal pigment was myoglobin, a definite peak at 581 mμ being present.

As soon as the pigmenturia began salicylates were administered, which lowered the temperature promptly. Sodium bicarbonate in large doses was also given. The patient continued to have backache and some general malaise for two days. Excretion of dark urine continued for four days, during which time the patient lost six pounds in weight despite adequate food and fluid intake. The urinary output never dropped below 1,500 c.c. in any 24 hour period, and averaged 2,000 c.c.; the specific

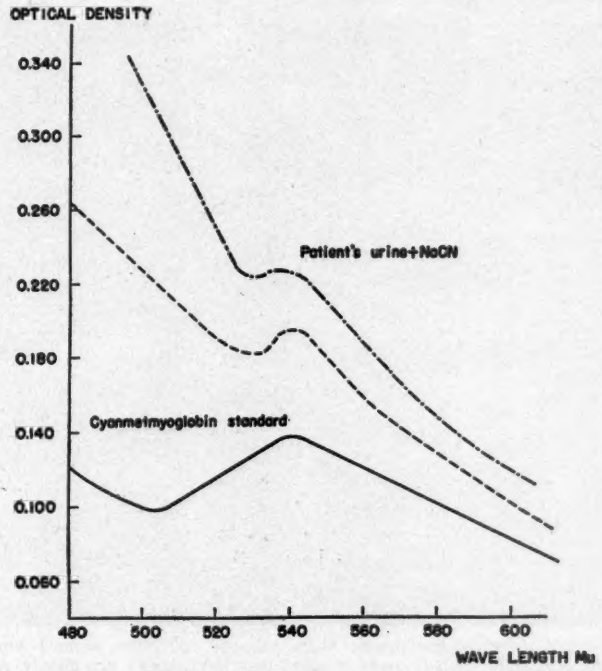

FIG. 2. Spectrophotometric analysis of the patient's urine with added sodium cyanide. A standard cyanmetmyoglobin preparation is included for comparison.

gravity remained about 1.017. The urinary pH rose to a maximum of 8.0 over the four-day period. On the second day many red blood cells and red cell casts appeared in the urine. The reddish brown color gradually faded from the urine; four days after onset of pigmenturia, only minimal myoglobinuria was present. The plasma hemoglobin at this time was 9.7 mg. per 100 c.c. Other studies obtained during the period of decreasing pigment excretion revealed the bleeding (Duke), clotting (Lee-White) and clot retraction times to be normal. The prothrombin time was 100%; platelet count (indirect), 200,000 per cubic millimeter; blood urea nitrogen, 16 mg. per 100 c.c.; plasma creatinine, 1.3 mg. per 100 c.c. The endogenous creatinine clearance was 127 c.c. per minute; urea clearance, 57.3 c.c. per minute; urinary creatinine excretion, slightly elevated. A prothrombin consumption time

was 22 seconds. Slight albuminuria and microscopic hematuria persisted for over one month after cessation of the pigmenturia.

Approximately two months after the episode described above the patient developed an inguinal hernia. He was readmitted for surgical correction. Preoperative urines contained no albumin and only a few cells. No abnormal pigment was present. He was started on sodium bicarbonate four days prior to surgery. Under spinal anesthesia, a right inguinal herniorrhaphy was performed. At this time a section of internal oblique muscle was removed for pathologic examination. Six hours postoperatively his temperature rose to 100° F. for several hours. Nine hours later the urine became brown and continued to be dark for the remainder of that day. It contained only rare white cells and neither red cells nor albumin. Myoglobin was

FIG. 3. Several representative muscle fibers enlarged 630 times, stained with Schiff's periodic acid stain. No necrosis is seen; muscle striations are clearly visible.

again found in the urine (figures 1 and 2). The muscle biopsy showed well striated fibers without atrophy or inflammatory change (figure 3). A moderate amount of strainable lipoid was present as tiny droplets between muscle fibers (figure 4). Urinary coproporphyrin excretion was 73.36 μg per liter.

The dark urine was present only transiently; the patient recovered from the surgery uneventfully. He has been maintained on full duty without further febrile episodes; no muscle weakness, weight loss or dark urine has been present despite participation in occasional routine calisthenics and competitive sports.

COMMENTS

Myoglobinuria in this case followed elevation of the body temperature on five separate occasions. Two episodes, induced either by injection of typhoid vaccine or by a surgical procedure, were observed personally and con-

firmation of the myoglobinuria was obtained. In three instances, myoglobinuria was deduced from information supplied by the patient. The fever in all five instances was related to appropriate external stimuli (infection, inoculations or a surgical procedure), and did not appear to herald the onset of spontaneous myoglobinuria. The patient could not recall any febrile sensations or demonstrable fevers since 1953 except those mentioned in the protocol. The duration and quantity of myoglobin excretion appeared to vary directly with the height of the fever.

FIG. 4. Representative section of muscle fibers stained with Sudan IV and enlarged 130 times. The dark staining material is sudanophilic lipoid droplets lined up between muscle fibers. This finding is of unknown significance.

In the reported cases of idiopathic myoglobinuria the possibility of febrile precipitation of the acute attack is difficult to confirm. In one patient [14] the terminal episode was associated with inflamed tonsils, but fever was not recorded until after extremity pain supervened. In another case [26] the patient had had a respiratory infection a week previously but was apparently afebrile at the time muscle pain began. In several other cases, infection and fever were noted early in the course of the illness,[8, 9, 11, 21, 29] but myoglobinuria did not clearly follow temperature elevations. In a single case,[27] muscle pain and myoglobinuria followed a surgical procedure (appendectomy), but prodromal symptoms of the acute attack had already begun prior to surgery.

Several painstaking descriptions of the muscle lesion during or after an attack of myoglobinuria have been published; [27, 30] in one article [30] the histologic features of the skeletal muscle lesion were reviewed and summarized. The reader is referred to these descriptions. The variability in intensity of morphologic altera-

tions was ascribed to the apparent non-uniformity of muscle involvement and the severity and chronology of the attack. In the present case the muscle was normal, with only a slight increase in sudanophilic material in some fibers. The latter finding is of doubtful significance. In view of the lack of localizing muscular symptoms or signs, the biopsy site was chosen on the basis of accessibility during surgical repair of a hernia. The biopsy was obtained two symptom-free months after an episode of myoglobinuria, and preceded an attack by about nine hours. Another author [17, 23] has described relatively normal muscle during a symptom-free interval, though others [30] have found typical changes after prolonged remission.

The work of Ono suggests that relatively slight myoglobinuria may follow the quasi-physiologic muscular stress of marathon racing or convulsions. Whether sensitive methods will demonstrate similar myoglobinuria after fever is unknown at present. The present case must be considered paroxysmal myoglobinuria by definition. However, the absence of muscle pain or tenderness, the ability of the patient to tolerate severe muscular exertion without impairment, the absence of muscle atrophy and the negative muscle biopsy suggest a distinct difference from classic paroxysmal myoglobinuria. The latter may be considered muscle necrosis of unknown etiology, myoglobin liberation representing a consequence of the necrosis. As in Ono's cases, where red urine was excreted after running, the present case may be merely a quantitative extension of a normal process. Renal damage probably varies directly with the quantity of myoglobin excreted. The factors responsible for the unusually large myoglobin liberation are not known, nor is the apparent recent onset of febrile myoglobinuria in this patient explicable.

The recent increase of reports of idiopathic myoglobinuria suggests that the disease is not so rare as has previously been suspected. Spaet, Rosenthal and Dameshek [24] have discussed the differential diagnosis of paroxysmal pigmenturia. This clinical approach was of value in our initially suspecting myoglobinuria in the present case, and is worthy of being summarized briefly.

Myoglobin, being a heme pigment, will impart a positive benzidine test to the urine. In addition, the renal threshold for myoglobin is about 15 mg. per 100 c.c. (as contrasted to 100 to 150 mg. per 100 c.c. for hemoglobin). In the presence of dark red to brown urine, therefore, the absence of discoloration of the plasma will provide good support for ruling out hemoglobinuria. The positive benzidine reaction and absence of fluorescence of the urine under ultra-violet light would rule out porphyria. Microscopic examination of the urine would establish whether hematuria sufficient to so discolor the urine is present. In the absence of such massive hematuria, myoglobinuria is the diagnosis of choice; final proof requires spectrophotometric study of alkalinized urine. Though oxymyoglobin can be identified by this technic, conversion of the oxymyoglobin to carboxymyoglobin and cyanmetmyoglobin with appropriate agents will further confirm the diagnosis. In the absence of a change in urine color, more sensitive methods may be required to detect myoglobinuria.

Summary

A case of myoglobinuria following spontaneous and induced fever on five occasions is described. Review of the 28 previously reported cases of idiopathic

paroxysmal myoglobinuria reveals that fever occasionally precedes the signs and symptoms of myoglobinuria. Precipitation of myoglobinuria episodes by elevated body temperatures has never hitherto been noted. No explanation for this sequence of events is offered. It is suggested that small amounts of myoglobin may frequently be excreted after strenuous exertion or fever. Rarely, larger quantities may be excreted under the same circumstances. This type appears to differ etiologically, clinically and pathologically from classic paroxysmal myoglobinuria. Understanding of all forms of idiopathic myoglobinuria must await further unraveling of myoglobin metabolism.

ACKNOWLEDGMENT

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SUMMARIO IN INTERLINGUA

Myoglobinuria in humanos es associate con trauma de musculo striate per contusion, con occlusion arterial, e con electro-choc a voltage elevate. In plus, myoglobinuria occurre in un numero de mal-definite situationes clinic, incluse morbo del Frisches Haff (que es un geographicamente localisate acute morbo epidemic del musculos) e idiopathic myoglobinuria paroxysmal, con o sin atrophia muscular.

Usque al tempore presente, 28 casos de idiopathic myoglobinuria paroxysmal ha essite reportate. Dece-octo esseva provate per spectrophotometria. Le alteres es acceptate super le base de persistente manifestationes clinic, pathologic, e laboratorial. A causa del variabile aspectos clinic—probabilemente relationate al variabilitate del etiologia—plure systemas de classification ha essite proponite. Nulle se ha provate completemente satisfactori.

Ha occurrite plure casos de myoglobinuria que resimilava dermato-myositis in lor aspecto clinic e in lor curso. Altere casos de myoglobinuria esseva associate con un chronic forma muscular que resimilava dystrophia muscular, ben que differentias pathologic inter le duo morbos ha essite describite. In le majoritate del casos, myoglobinuria esseva precipitate per exercitio o un convulsion. Exposition a frigido e jejunation esseva presente non-systematicamente.

Plus sensibile methodos pro le detection de myoglobina ha demonstrate que micre e a vices grande quantitates de myoglobina pote esser excernite post exercitio effortiose. Ben que febre ha nunquam essite considerate como un causa de myoglobinuria, illo precede a vices le excretion de myoglobina in le urina. Tamen, in le majoritate del casos il non es possibile establir un clar nexo de causa e effecto inter febre e myoglobinuria.

Es reportate un caso de myoglobinuria occurrente a duo occasiones post febre inducite e historicamente a tres occasiones post febre spontanee. Le patiente esseva in servicio militar; le attaccos le incapacitava solmente brevemente; e ille se restabliva sin apparente injuria residue. Un biopsia muscular, effectuate duo menses post un attacco de myoglobinuria e plure horas ante un altere esseva normal.

Le pathologia muscular de myoglobinuria es mentionate. Es includite referentias al experientia de altere autores in lor effortio de obtener normalitate muscular.

A causa de differentias in le aspectos clinic inter le caso hic presentate e le usual idiopathic myoglobinuria paroxysmal e, in plus, a causa de similaritates inter le presente caso e le typo de myoglobinuria vidite post effortio, il es stipulate que myoglobinuria pote occurrer sub diverse circumstantias. Un es un morbo marcate per necrose muscular; un altere es un extension de un processo quasi-physiologic.

Plure simple tests laboratorial que es disponibile pro le diagnose differential de pigmenturia paroxysmal es describite brevemente. Lor uso pote resultar in un diagnose presumptive de myoglobinuria. Usualmente, diagnoses absolute require spectrophotometria.

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CIRCULATING FIBRINOLYSIN IN A CASE OF PROSTATIC CARCINOMA WITH BONY METASTASES *

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During the last few years sporadic cases of afibrinogenemia and hypofibrinogenemia have been appearing in the literature. Diminished levels or total lack of fibrinogen has occasionally been noted as a congenital abnormality,[6, 17] but usually this disturbance in hemostasis is acquired. The earliest recorded cases were reported in shock, or in hemorrhagic,[1, 24] traumatic [24] or anaphylactic response to antigens.[24] A decrease of plasma fibrinogen levels has been noted in cases of severe liver necrosis from phenobarbital and methyl alcohol [34] and chloroform.[24] More recently, afibrinogenemia has been reported following pulmonary operations,[15] in preëclampsia, the first day of menstruation,[35] amniotic fluid embolus,[18] premature placental separation [16, 32, 33] and long-standing intra-uterine death.[5, 13, 19, 31] As a factor accompanying malignant disease, the lack of fibrinogen has been noted with leukemia,[2] carcinoma of stomach and lung,[1] and in cases of carcinoma of the prostate with metastases.[4, 9, 12, 20, 26, 27, 28, 29] We have recently observed a fatal case of carcinoma of the prostate with afibrinogenemia due to the presence of a circulating fibrinolysin, and present the findings in this case report, together with a discussion as to probable etiology, course and treatment of the complication.

Case Report

A 68 year old Russian-born Jewish male hat salesman first entered St. Luke's Hospital as a patient of one of the authors (F. S.) on March 2, 1954. His complaint was the appearance of "black and blue spots" over his body for the 10 days prior to admission. He had been admitted to another hospital three years before, where a positive serologic test for syphilis had been found. He was adequately treated with penicillin. He was found to have carcinoma of the prostate at that time and a prostatectomy was performed. He was placed on Ethinyl estradiol (Estinyl), 0.02 mg. twice a day, which he took intermittently. Except for the demonstration of poorly functioning kidneys by pyelogram a few weeks prior to admission, he had been well until his present illness. Ten days before coming to St. Luke's Hospital he had experienced the onset of anorexia without any other gastrointestinal symptoms, and

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for the first time noted "black and blue" areas over his hands and arms without any antecedent trauma. He gave no history of hematuria, melena, bleeding gums, epistaxis or hematemesis. There had been no exposure to bone marrow depressants or toxins. He had had no sore throat, lymph node enlargement, cough, fever or weight loss. He also complained of transient bilateral shoulder pain, which subsided without any lesions being demonstrated by x-ray.

Physical examination revealed a temperature of 99.8° F. per rectum, a pulse of 72, respirations of 24, and a blood pressure of 190/60 mm. of Hg in a chronically ill appearing man who was nonicteric. He had ecchymotic areas 15 cm. in diameter over his left shoulder, 5 cm. in diameter over his right shoulder, and multiple smaller areas over his hands, chest and legs; all these areas were nontender. His buccal mucosa contained numerous petechia-like lesions. The neck was supple, there were no significant lymph nodes, the lungs were hyperresonant but clear, and the heart was slightly enlarged, with a regular rhythm and a harsh systolic murmur over the aortic area. There was no second aortic sound or transmission of the murmur into the neck. The liver was percussed 3 to 4 cm. below the costal margin; it was regular and nontender. No spleen or other masses or organs were felt, but a well healed suprapubic scar was noted. Neurologic examination was normal; rectal examination revealed a firm, irregular, nontender mass in the anterior rectal wall at the fingertip.

Initial laboratory studies consisted of a urinalysis showing a specific gravity of 1.006, with a 1 plus albumin, 0 to 5 red blood cells and 0 to 5 white blood cells per high power field. Hemoglobin was 8.7 gm./100 ml., with a red blood cell count of 3.00 million/cu. mm. and a white blood cell count of 7,700/cu. mm., with a normal differential, a platelet count of 157,000/cu. mm., and a reticulocyte count of 3.2%. He had a blood urea nitrogen of 19.3 mg.%, a blood sugar of 137 mg.%, an acid phosphatase of 23 Gutman units (normal, 1 to 4 units/100 ml.), an alkaline phosphatase of 23.7 Bodansky units (normal, 1 to 4 units/100 ml.), and a phosphorus of 3.5 mg.%. Electrocardiogram revealed a sinus rhythm, left axis deviation and left ventricular hypertrophy. Chest x-ray demonstrated an elongated but not dilated aorta and a moderately enlarged heart. Bone x-rays showed many areas suggestive of osteoblastic metastases. Sternal bone marrow aspiration was interpreted as showing hyperplasia of all elements, with an increase in the number of megakaryocytes.

Blood clotting studies included a venous clotting time of eight minutes (Lee-White), with a redissolution in one hour of the clots that were formed. Coagulation time (capillary blood) was five minutes 20 seconds; bleeding time, 30 minutes; prothrombin time, 17.6 seconds for whole plasma (normal, 12.6 to 13.8 seconds), and 48.2 seconds for the 12.5% plasma dilution (normal, 27.2 to 31.9 seconds), with a 50.5% whole plasma activity. On the clot retraction test there was no clotting in 24 hours, and serum prothrombin consumption test was 16.2 seconds (normal, greater than 30 seconds). Vitamin C level was 0/9 mg.% (normal, 0/4 to 1/0 mg.%), and blood fibrinogen level was 150 mg.% (normal, 300 to 400 mg.%), with a normal Rumpel-Leede tourniquet test.

On his third hospital day the patient experienced gross hematuria for the first time, and it was noted that a slight ooze of serosanguineous material continued from the site of his bone marrow aspiration. He was placed on estradiol, 10 mg. orally twice a day initially; then stilbestrol, 5 mg. orally three times a day, was substituted for this. He received 150 mg. of vitamin K oxide intravenously, and 1,000 c.c. of fresh whole blood. There was no response in his prothrombin mechanism to the vitamin K oxide. The hematuria ceased after three days, no new ecchymotic lesions appeared, and the ooze from the site of his bone marrow aspiration was controlled incompletely with topical thrombin.

The patient was discharged on the above dose of stilbestrol, with a hemoglobin of 9.6 gm./100 ml., a red blood cell count of 3.42 million/cu. mm., a platelet count of

162,000/cu. mm., a venous clotting time of 10 minutes with poor quality clot, and a prothrombin time of 19.6 seconds, whole plasma (normal, 12.6 to 13.8 seconds), 69 seconds for the 12.5% plasma dilution (normal, 27.2 to 31.9 seconds), with a 35% whole plasma activity.

The patient did well during the next 18 months, his liver receding in size, and on stilbestrol alone his prothrombin time gradually returned toward normal, until one month prior to his second admission, when it was noted that he again formed a soft quality clot. He had a whole plasma time of 15.5 seconds (normal, 12.6 to 13.8 seconds), with a 52% activity. The 12.5% plasma dilution could not be measured because of the lack of formation of a clot.

The patient's second admission, on September 30, 1955, followed three weeks of hematuria which had begun one week after an uneventful bilateral orchiectomy at another hospital. He had been passing small blood clots in his urine for three days but otherwise had no evidence of hemorrhagic diathesis by history. Aside from bilateral gynecomastia, a firm, regular, nontender liver palpated 4 cm. below the costal margin and a generalized "yellowish hue" to the skin, the physical examination was negative. A hemoglobin of 8.5 gm./100 ml., with a red blood cell count of 2.41 million/cu. mm. and an acid phosphatase of 16.4 (Gutman units), were the abnormal laboratory findings. The patient received 1,000 c.c. of fresh whole blood, with cessation of hematuria one day after admission, and was discharged four days later without further evidence of bleeding.

During the next three months the patient's prothrombin time remained prolonged (particularly the 12.5% plasma dilution time), and he intermittently complained of one- to two-day episodes of gross hematuria. He required 2,500 c.c. of fresh whole blood as an outpatient during this period to maintain his hemoglobin in the 9 to 10 gm. range, and one month prior to his last admission he was given 2.7 gm. of human fibrinogen, with an increase in his blood fibrinogen level from 188 mg.% to 250 mg.% (normal, 300 to 400 mg.%). His prothrombin time still remained 19 seconds for whole plasma (normal, 11.4 to 13.5 seconds), 69.3 seconds for the 12.5% plasma dilution (normal, 27.9 to 32.9 seconds), and 26.8% activity. At this time he also received radiation to his pituitary region through two temporal portals: left, 5,284 r to skin, 3,036 r to pituitary; right, 5,284 to skin, 3,128 r to pituitary.

For the last six months of his life he complained of severe bone pain, which was controlled only by large doses of narcotics, despite a slight diminution following his bilateral orchiectomy.

One week following his last transfusion (January 3, 1956), he entered St. Luke's Hospital semicomatose following 24 hours of severe melena and hematuria. Despite intravenous fluids, whole blood and oxygen, his blood pressure was obtainable only once—at 80/40 mm. of Hg—and he ceased breathing an hour following admission.

Summary of Autopsy Findings: A small portion of the prostatic carcinoma remained which extended directly into the prostatic urethra and urinary bladder, with secondary obstruction of both ureters, producing bilateral hydronephrosis and hydroureter with chronic pyelonephritis. The presence of focal acute myocarditis and hemorrhagic mucosal lesions of the small and large bowel led the pathologist to conclude that the patient had died in uremia.

There was evidence of the hormone therapy the patient had been receiving, with many of the tumor cells exhibiting pyknotic changes, increased staining density and naked nuclei. There was also bilateral gynecomastia. Secondary to pituitary radiation, the gland showed regressive changes both grossly and microscopically. The thyroid and adrenal glands were small and showed evidence of reduced function.

There were no liver, kidney or demonstrable pelvic lymph node metastases. There was extensive tumor infiltration into the vertebral marrow, with an increase in bony trabeculae reflecting an osteoblastic stimulus on the part of the tumor.

The heart and aorta were essentially normal aside from minimal arteriosclerotic changes, and the lungs were unremarkable.

Comment

The patient's operations were performed at another hospital, but all complaints referable to his hemorrhagic diathesis were treated at St. Luke's Hospital. Many studies were done to determine the cause or to discover the abnormal factor responsible for his bleeding. It became evident that he was forming a soft clot and also that the clot he formed was soon dissolved. The presence of hypofibrinogenemia was demonstrated; a fibrinolysin was postulated as the underlying mechanism because of the lysis of the clot. The bleeding tendencies were fairly well controlled for a year and a half by estrogenic hormone therapy alone, but as

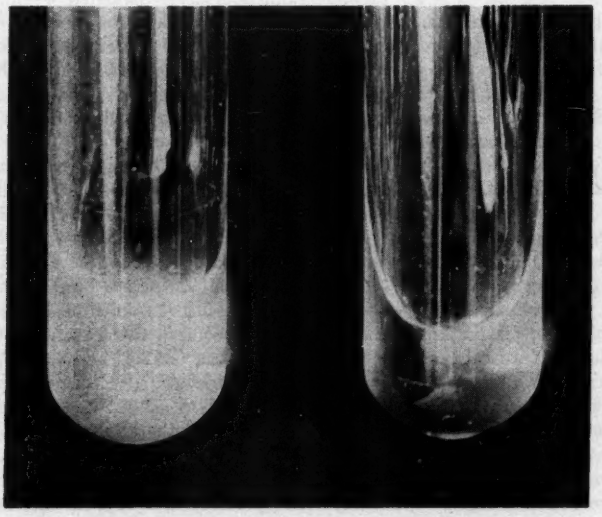


Fig. 1. Comparison of plasma and clot formation. Control (left) and S. D. (right).

the disease became more widespread and his general state deteriorated he seemed refractory to this despite bilateral orchiectomy. In a last attempt to slow the progress of the disease, pituitary irradiation after the recommendation of Murphy [14] was attempted, with no demonstrable alteration in the course. He had lived nearly five years from the time he was first found to have a carcinoma of the prostate which was considered inoperable. Until the last episode, his manifestations of a bleeding tendency were never severe and for the most part were controlled by close periodic blood counts, prothrombin time determinations and whole blood as needed. Due to the scarcity of human fibrinogen and its need in obstetric emergencies, this was used in a small amount on only one occasion to aid in terminating a prolonged period of hematuria. A simple method of following this man's course was the observance of his plasma clot, either alone or compared to a normal control (figure 1); this method was used as a gross evaluation during office visits.

We continually noted the importance of the 12.5% plasma dilution prothrombin time in evaluating this patient's fibrinolytic activity. This value would often be greatly prolonged in the face of near-normal whole plasma values. The decreased percentage of fibrinogen in the diluted plasma was undoubtedly the

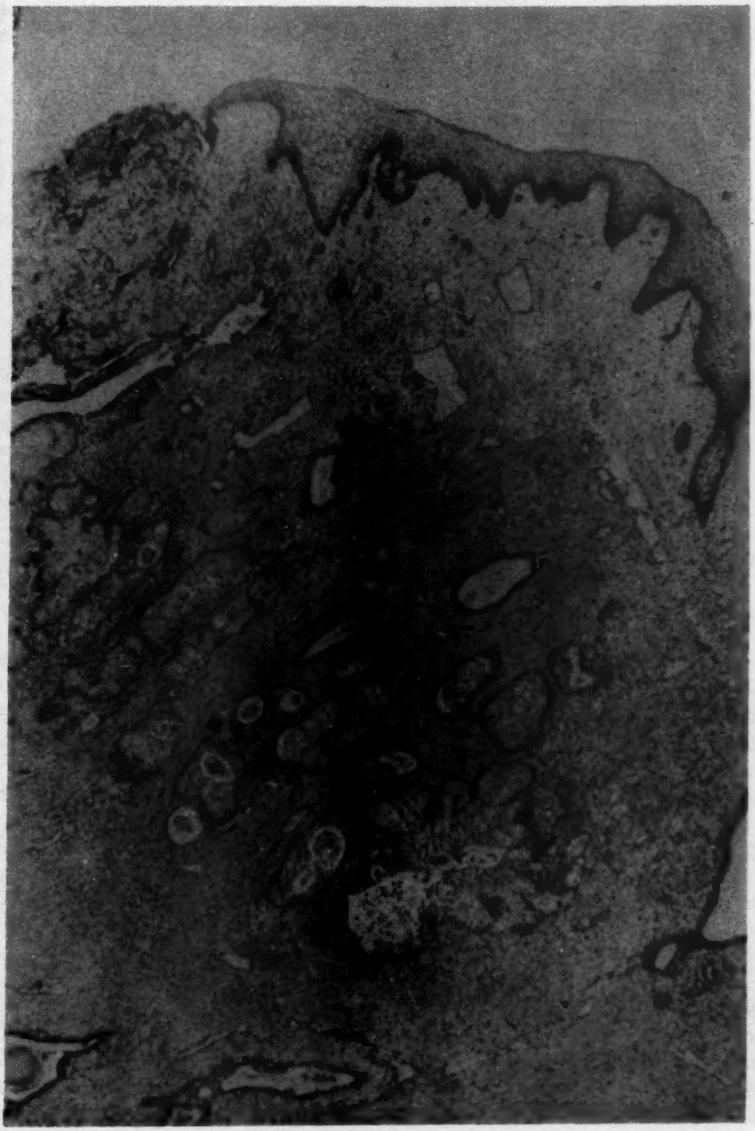


FIG. 2. A section from the adenocarcinoma of the prostate in the reported patient with a fibrinolysin and hypofibrinogenemia treated with estrogenic hormones.

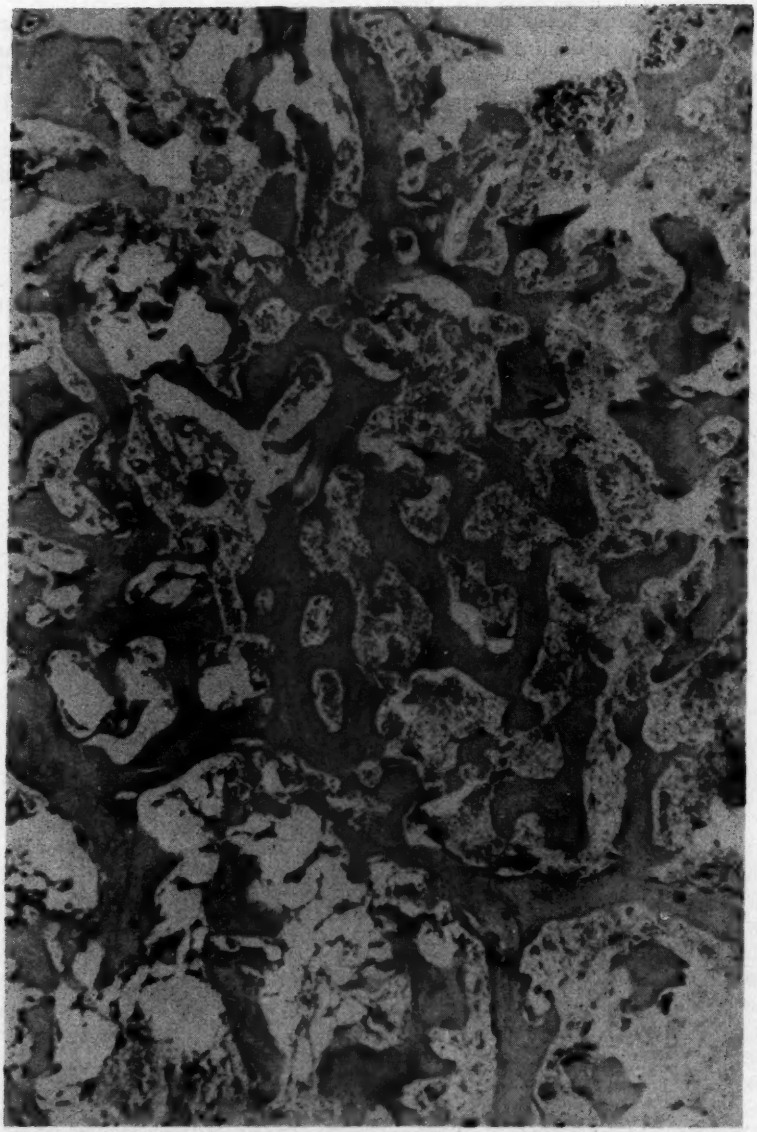
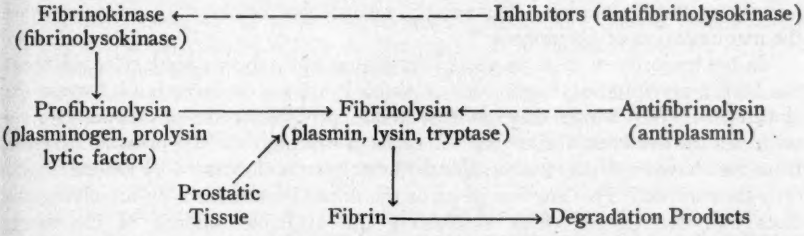


FIG. 3. Osteoblastic (vertebral) adenocarcinoma metastases from the prostate in the reported patient.

reason for this prolongation which, on one or two occasions, was so severe that no clot formed. Thus one can use the 12.5% plasma dilution time as a more accurate indirect measure of the presence of a fibrinolysin and/or the level of hypofibrinogenemia.

Discussion

Normal blood contains the precursor of fibrolysin in the form of profibrinolysin. This is thought to be activated by fibrinolysokinase, but usually is held in check by blood inhibitors of both fibrinolysokinase and fibrinolysin.[10] Thus when there is an increase in the activation of profibrinolysin, or when there is a decrease in the inhibitors, we can see an increase in fibrinolytic activity, as is demonstrated by the diagram of Stefanini:[23]



These fibrinolysins are similar to those found in tissue and bacteria,[10] as was first demonstrated in 1933 by Tillett and Garner in the hemolytic streptococcus.[30] The first case of congenital afibrinogenemia is referred to by Prentice,[17] and was reported by Rabe and Solomon in 1920. Ten years later Jürgens and Trautwein[9] first realized that a fibrinolysin was the basis of hypofibrinogenemia in one of their patients with adenocarcinoma of the prostate with metastases. They measured the fibrinogen level of the blood and found it to be 60 mg.%.

Huggins and Neal[7] in 1942 demonstrated that human semen had both fibrinogen and thromboplastin that would cause the semen to clot after approximately 10 minutes. They could not demonstrate trypsin in all samples of human prostatic fluid, but noted that these clots would slowly lyse over the next few hours. This material seemed similar to the fibrinolysin that Tillett and Garner[30] had isolated in the hemolytic streptococcus, as it too would slowly lyse a blood clot and could be destroyed on heating at 70° C. for five minutes. Huggins and Vail[8] strengthened this concept in 1943 when they demonstrated that a proteolytic enzyme different from trypsin was present in the prostatic secretion of man, and that this enzyme was capable of digesting fibrinogen and fibrin. They thought that this was similar to fibrinolysin.

In 1948 MacFarlane and Biggs,[11] studying fibrinolysin, realized that activators of profibrinolysin or proplasmin were released in tissue damage. Tagnon[25] in 1942 demonstrated a fibrinolysin in chloroform-extracted serum which decreased prothrombin, fibrinogen and fibrin, and since then, with Shulman,[21] has demonstrated its activity by a tagging technic. He also found that it prolongs the prothrombin time by decreasing the above and the AC globulin factor.[29]

In 1949 Marder et al.[12] presented a case of carcinoma of the prostate with no clot formation and no fibrinogen demonstrated in the blood on two occasions. Seale et al.[20] in 1951 demonstrated a fibrinogen level of 21 mg.% under similar circumstances, while Tagnon et al.[26, 27] demonstrated the presence of a proteolytic enzyme in two cases of carcinoma of the prostate with metastases. The occurrence of extensive metastases, especially to bone, in these cases prompted Tagnon[28] to investigate the correlation with the acid phosphatase level, without

any definite relationship being established. He demonstrated that this proteolytic enzyme was present in normal, carcinomatous and metastatic prostatic tissue.

In 1955 Tagnon [29] showed that both the plasma and the prostatic tissue extracts from patients with carcinoma of the prostate will cause clot dissolution in approximately 12% of those with the disease. Dolaz et al.[4] recently reported a case in which fibrinolytic activity seemed to decrease on stilbestrol treatment, as previously established by Tagnon.[29] This was indicated, as in our case, by a return of the prothrombin time to normal and a failure to demonstrate fibrinolytic activity by clot dissolution. Conversely, testosterone has been shown to increase the manifestation of fibrinolysis.[29]

In the majority of cases in which circulating fibrinolysins were released, there has been a precipitating factor such as shock,[24] anoxia or excessive intravascular clotting,[18, 19, 33, 34] which may either activate profibrinolysin or fibrinolysin, or utilize all the available fibrinogen. In cases of carcinoma of the prostate it seems, from the above evidence, that an actual fibrinolysin is elaborated by the carcinoma cells themselves. This enzyme disturbs the normal mechanism by dissolving any clots that are formed, thus exhausting the available amount of circulating fibrinogen and fibrin. The constant formation and dissolution of clots is a drain on the supply of fibrinogen and fibrin.

The established treatment of carcinoma of the prostate with fibrinolysis remains estrogens and orchiectomy for the neoplasm, with blood replacement and fibrinogen as needed with other supportive measures. The efficacy of pituitary irradiation cannot at present be evaluated and must await further study.

Summary

A case is presented of prostatic carcinoma with bony metastasis and a demonstrable circulating fibrinolysin causing hypofibrinogenemia. The mechanism and possible effect of this enzyme are discussed.

Acknowledgment

We wish to thank Dr. Charles Begg for permission to use the autopsy findings, and Mr. Albert DeNatale for his assistance in clotting mechanism studies.

Summario in Interlingua

Un revista del recente litteratura medical revela rar casos de hypofibrinogenemia. Iste constatation pote haber un base congenite, sed usualmente le phenomeno es secundari a choc, necrose hepatic, operationes pulmonar, preeclampsia, le prime die de menstruation, embolo de fluido amniotic, prematur separation placental, e morte intra-uterin de presentia prolongate. In casos de malignitate, basse nivellos de fibrinogeno ha essite notate in leucemia e carcinoma pulmonar, gastric, e prostatic.

Es reportate le caso de un masculo blanc de 68 annos de etate con inoperabile adenocarcinoma del prostata con metastase ossee, in qui esseva demonstrate le presentia de un fibrinolysina apparentemente elaborate per le carcinoma. Ben que le patiente experientiava episodios de sanguination durante le ultime annos de su vita, ille viveva circa cinque annos post le momento del diagnose. Le studio del coagulation revelava le sequente anormalitates: Redissolution del coagulate sanguine venose un hora post le formation del coagulo; prolongation del tempore prothrombinic con le plasma in dilution de 12,5%; nulle retraction de coagulo; e augmentate consumption de prothrombina. Le nivellos de fibrinogeno del sanguine esseva repetitemente basse. A un occasion le patiente recipeva integre fibrinogeno human, sed

usualmente ille esseva tractate con sanguine fresc e con estrogenos. Como mesura final, le patiente esseva subjicite a irradiation pituitari, sed sin apparente effecto super le curso del morbo.

Le manifestationes sanguinatori in le prime phases del morbo de iste patiente esseva ben regulate post le institution del therapia a hormones. Duo facilemente disponibile methodos esseva usate pro tener le activitate fibrinolytic in su sanguine sub observation. Nos poteva (1) comparar le formation de coagulo in su caso con illo de un subjecto de controlo sub le conditiones de temperatura standard de interior o (2) determinar le tempore prothrombinic con plasma diluite a 12,5%. Iste ultime esseva frequentemente multo prolongate quando le tempore integre esseva normal. Isto resultava del reducite nivello de fibrinogeno in le plasma diluite, i.e. un nivello insufficiente pro contribuer al mechanismo coagulatori.

Enzymas proteolytic esseva demonstrate in semine human 16 annos retro, in secretiones prostatic 13 annos retro. Metastases ossee ab adenocarcinoma del mamma, adenocarcinoma prostatic, e normal histos de prostata, omne istos forma genuin fibrinolysinas in quantitates descendente, sed nulle correlation ha essite establite inter iste facto e le phosphatase acide del sero. Circa 12% del patientes con adenocarcinoma del prostata ha demonstrabile nivellos de fibrinolysinas in le circulation. Iste fibrinolysinas—o al minus lor formation—es apparentemente inhibite per le therapia a estrogeno. Tal enzymas preveni coagulation per dissolver le coagulo normal, con le resultante reduction del disponibile quantitates de fibrinogeno e fibrina circulante.

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SURGICAL MANAGEMENT OF SICKLE CELL ANEMIA: THE USE OF PACKED RED BLOOD CELL TRANSFUSIONS*

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The presence of sickle cell anemia complicates the management of surgical patients and makes surgery more hazardous.[1] A method of preparation of patients with sickle cell anemia for surgery by the use of packed red blood cell transfusions will be presented, with a case report demonstrating some of the specific problems of management.

Case Report

A 25 year-old, 120 pound Negro woman with sickle cell anemia was first admitted to another hospital on March 18, 1955, with a diagnosis of far advanced, active pulmonary tuberculosis with a large cavity in the upper lobe of the left lung. Her symptoms of anorexia, weakness, sweats and productive cough had begun three weeks prior to admission. Physical findings at that time revealed a blood pressure of 120/60 mm. of Hg, pulse 110, and temperature 101° F. The mucous membranes were pale. There was moderate cardiomegaly, a grade II systolic apical murmur, and an accentuated pulmonic second sound. There were dullness to percussion and coarse moist râles in the upper lobe of the left lung. The hemoglobin was 4.7 gm.% at this time, with a reticulocyte count of 5.5%. Numerous acid-fast bacilli were found in the smear of her sputum.

The patient was started on antituberculous therapy and given 1,500 c.c. of whole blood, and in approximately two weeks her temperature was normal and she was clinically improved. Because her sickle cell anemia became a problem in management, she was transferred to the Department of Pulmonary Diseases of the Philadelphia General Hospital (Blockley Division), on the service of Dr. David Cooper. At this time the physical examination confirmed the previous findings, and the chest x-ray showed a single, thick-walled cavity, 3 cm. in diameter, in the apex of the upper lobe of the left lung. Surgery was considered in October, 1955, but it was decided that the patient was too poor an operative risk. Laboratory findings at this time consisted of a hemoglobin of 5.4 gm.% (table 1), with sickled cells seen on the peripheral blood smear, an S-S electrophoretic pattern (figure 1A), a white blood cell count of 10.8 thousand/mm^3, a reticulocyte count of 26.4%, a serum bilirubin of 2.46 mg.%, of which the one minute fraction was 0.59 mg.%, a blood urea nitrogen of 63 mg.%, a blood creatinine of 2.4 mg.%, a urinary specific gravity of 1.010 or under, and a phenolsulfonphthalein test of 15% excretion in 15 minutes and 55% in two hours.

In December, 1955, it was decided to transfuse the patient with compatible, nonsickling, Coombs' cross-matched, packed fresh red blood cells in order to prepare her for surgery. She received the packed cells of two units of blood on December 20, 1955, two units on December 21, and one unit on December 22, thus bringing her hemoglobin to 14.9 gm.% and reticulocyte count to 7.0% on December 23. Each unit of cells was given over a period of several hours. At no time during the trans-

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fusions did the patient experience any transfusion reactions or symptoms of hypervolemia. She was, in fact, symptomatically improved after the transfusions. On December 27, one week after the initial transfusion, the reticulocyte count was 0.3%, and it remained at this level until the time of surgery. No further transfusions were given until January 6, 1956, at which time the hemoglobin was 12.2 gm.%, and the packed cells of one unit of blood were given. Following this, only an occasional sickled form could be seen on the sickle cell preparation (done by the sodium metabisulfite, 2% method), and the electrophoretic pattern was that of a sickle cell trait (figure 1B).

TABLE 1

Laboratory Data

Dates	Hemoglobin (Gm. per 100 c.c.)	Retic. Count	No. of Units of Packed RBC's	Serum 1′	Bilirubin Total
September 20	6.9			0	2.10
November 11	5.4	26.4			
December 19	4.8	17.8			
December 20			2 units		
December 21			2 units		
December 22	12.5	10.8	1 unit*		
December 23	14.9	7.0		0.59	2.46
December 27	13.5	0.3		0.14	0.44
January 5	12.2	0.2		0.06	0.20
January 6			1 unit		
January 9	13.1				
January 10			1 unit &**		
January 11	12.1				
January 13	11.4				
January 19	9.6	1.2	1 unit*	0.20	0.60
January 20	11.4				
January 29	10.5	0.2			
February 6	10.2	1.4			
February 16	8.5	6.8			
March 15	7.2	13.9		0.22	2.01
April 10	6.5	7.4		0.22	2.80

* Transfusion given after determination of hemoglobin for that day.
** 700 c.c. of whole blood.

On January 10, 1956, under cyclopropane anesthesia,* a left upper lobectomy was performed.† During the procedure the patient received 700 c.c. of whole blood (an amount equivalent to the estimated blood loss), and the evening after surgery she received one unit of packed red blood cells. Postoperatively the patient was oliguric, and the blood pressure was 90/60 mm. of Hg. On the second postoperative day, serum electrolytes were as follows: sodium 115 mEq./L.; chlorides, 94 mEq./L.; potassium, 5.1 mEq./L.; carbon dioxide combining power, 14.9 mEq./L. The patient was given 120 c.c. of one molar lactate intravenously over a two hour period, with a gradual rise in blood pressure to her normal preoperative level. The urinary output rose to normal, and the rest of the postoperative period was uncomplicated. The day following surgery the hemoglobin was 12.1 gm.%. The patient received no further transfusions until January 14, 1956, at which time the hemoglobin was 9.6 gm.% and the reticulocyte count 1.2%.

The patient was discharged on February 23, 1956, and when she was seen on April 10, 1956, the hemoglobin had fallen to 6.5 gm.% and the reticulocyte count had

* Anesthesiologist: Dr. E. H. Conner, Chief of the Department of Anesthesia.
† Surgeon: Dr. Thomas J. E. O'Neill.

risen to 7.4%. There were no sickle cell crises from the time the transfusions of packed cells were started until the most recent examination, in April, 1956.

Discussion

Sickle cell anemia is associated with an abnormal [S] hemoglobin, which differs from normal hemoglobin electrophoretically;[2] patients with sickle cell anemia have a large percentage of [S] hemoglobin and an absence of normal [A] hemoglobin. The formation of the abnormally shaped sickle cells is probably

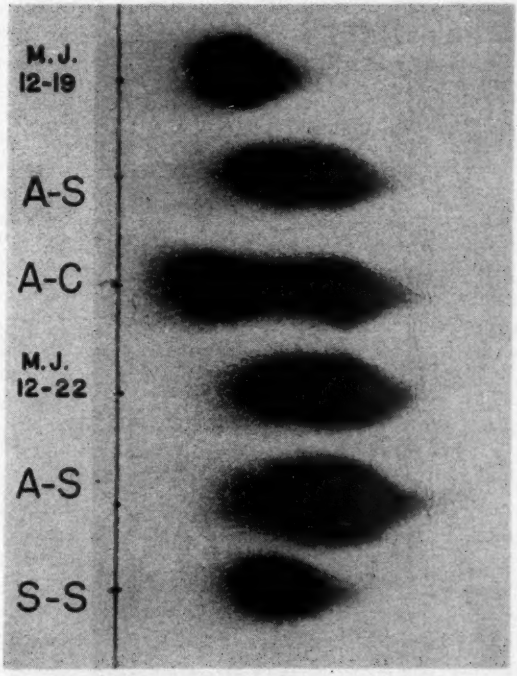

Fig. 1A. Hemoglobin electrophoresis. ("M. J." refers to the patient.) Dates of patient's blood examination are found under her initials. Other letters represent type of hemoglobin (controls).

due to the molecular orientation of the intracellular [S] hemoglobin,[3, 5] and occurs under conditions of decreased oxygen tension,[6, 8] and is favored by a lowering of the pH [9] and by hypertonic sodium chloride.[9] Decrease in oxygen tension also increases the viscosity of blood in patients with this disease, and this is directly related to the number of sickled forms.[8] Mechanical fragility is also increased by deoxygenation.[8, 9] All of these changes occur in physiologic ranges of oxygen tension.

The pathophysiology of sickle cell disease may be explained by the concept that the molecular orientation is basic to the structural mechanism of the sickling process.[3] The abnormality in the red blood cells is believed to be responsible for

the multiple vascular occlusive phenomena and also for the hemolytic anemia. Diminution in oxygen tension locally in the tissue, aggravated by decreases in pH and slowing of the circulation, may cause sufficient numbers of red blood cells to assume the sickled form so that blood viscosity increases. The increased viscosity further slows blood flow, thus starting a vicious cycle of sickling and erythrostasis, which ultimately may lead to capillary congestion and ischemic infarction.[1, 10]

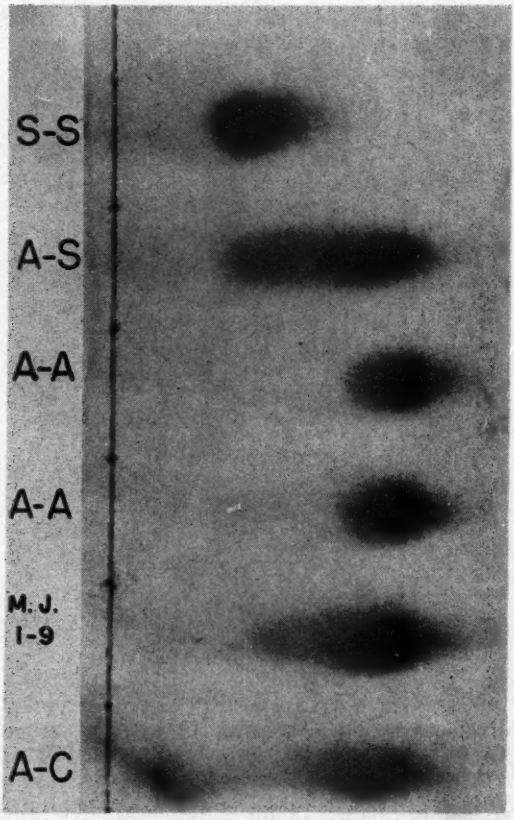

FIG. 1B.

After stasis of red blood cells, a certain number become fixed in the irreversibly sickled form and have an increase in mechanical fragility. This increased fragility may be the cause of the shortened life span and thus the hemolytic anemia.

It has been shown that normal red blood cells transfused into patients with sickle cell anemia have a normal survival time, whereas transfusions of sickle cell anemia cells into normal patients have a diminished survival time.[11, 12] This is

further proof that the pathogenetic principle operating in the disease resides within the red blood cell.

Sickle cell anemia increases the risk associated with surgical procedures for two reasons. First, the anemia is usually severe, and many of the manifestations of sickle cell disease are due to anoxemia. Second, because of the inherent abnormality of the red blood cells in these patients, the vicious cycle of erythrostasis and ischemic infarction is likely to be accentuated by surgery and crises are likely to occur. Slight changes in oxygen saturation, pH or osmolarity may precipitate sickling and start the cycle. In addition, organic changes in such vital organs as the heart, lungs, liver and kidneys [13] are characteristic of the disease and add to the risk. Possibly of special interest in this case are the renal functional abnormalities which occur in this disease. The earliest change is the inability to concentrate urine; [14, 15] later, glomerular changes occur, and azotemia may ensue.

It was felt by the authors that the patient's prognosis with the combination of sickle cell anemia and a tuberculous cavity was poor.[16] Further, we felt that by giving repeated transfusions of normal packed red blood cells, the anemia could be corrected, erythropoiesis depressed, and thus the number of sickled erythrocytes reduced.[17] Since the life span of sickled erythrocytes is considerably less than normal, the number of these cells in the peripheral blood should decrease rapidly after bone marrow production is depressed. By continuing to maintain a normal erythrocyte count by giving repeated transfusions, erythropoiesis may be depressed indefinitely and normal healing may occur, since normal transfused cells will not participate in the sickling, increased mechanical fragility, and increased blood viscosity.

In this case the anemia was corrected within three days by giving five units of packed red blood cells (table 1). Packed red blood cells were given rather than whole blood to avoid overloading of the circulation. Furthermore, it is possible that the additional plasma protein might increase the osmolarity of the patient's blood and thereby increase the tendency toward sickling. One week after the first transfusion the hemoglobin was 13.5 gm.%, the reticulocyte count was 0.3%, and the total bilirubin was 0.20 mg.%. The reticulocyte count remained below 1% as long as the hemoglobin was maintained above 10 gm.%. Additional transfusions of packed red blood cells were given when needed to maintain the hemoglobin at a level sufficient to keep bone marrow production depressed. Before transfusions the electrophoretic pattern was [S–S] (figure 1A), but at the time of operation the pattern was [A–S] (figure 1B), with a predominance of [A], and a sickle preparation showed only a rare sickled form. Microscopic examination of the resected tissue showed only rare sickled cells in the vessels.

Postoperatively the patient developed prolonged oliguria associated with hypotension, and on the second postoperative day the serum sodium was found to be 115 mEq./L. Simultaneous with the replacement of the sodium intravenously, the blood pressure rose to normal preoperative levels and the urinary output rapidly increased to normal. It is possible that excess loss of sodium during surgery, coupled with the patient's inability to conserve sodium, may account for the oliguria. The patient tolerated surgery without crisis, and postoperative healing progressed normally. After healing had progressed suffi-

ciently the hemoglobin was allowed to drop to pretransfusion level, and the patient was discharged.

The administration of blood is not without risk. Rapid infusions may precipitate congestive heart failure. The possibility of serum hepatitis remains a consideration in any transfusion. Repeated transfusions, especially in the presence of a hemolytic process, has been implicated by some in the pathogenesis of hemosiderosis.[18, 19] The most serious complication is the possibility of transfusion reactions. This is especially true in patients with sickle cell anemia, in whom the possibility of sensitization is increased by the great number of transfusions they may be given.

By preparing selected patients for elective surgery by giving transfusions in order to maintain a normal hemoglobin, the authors believe the risk of surgery is greatly diminished and healing greatly accelerated. In emergency surgery the anemia should be corrected if possible. This procedure not only eliminates the anemia, but also diminishes the percentage of sickled forms by dilution, thus decreasing the risk of crisis during surgery.

Another possible place for the use of repeated transfusions is in the healing of intractable leg ulcers.[20]

According to some reports, sickle cell anemia in pregnancy increases the risk to both mother and baby.[21, 23] Obstetric complications are increased. Crisis has been reported most frequently in the last trimester.[24] Recently, patients with sickle cell variants have been noted to have severe crises in the last trimester of pregnancy.[25] If this is confirmed, it may be advantageous to give transfusions during the last trimester to prevent some of these serious complications. Further evaluation of patients with sickle cell anemia and variants during pregnancy is being undertaken.

Summary and Conclusions

1. The signs and symptoms in patients with sickle cell anemia are due to the anemia plus occlusive vascular phenomena secondary to sickling of the red blood cells, and are probably caused by an inherent abnormality in the red blood cells. Decreased oxygen tension, lowering of the pH and increase in osmolarity may increase the tendency to sickling, and a vicious cycle of erythrostasis may ensue.

2. Patients with sickle cell anemia are notably poor risks for surgery. The conditions present during surgery and in the postoperative period may precipitate sickling. By giving repeated transfusions of packed normal red blood cells, and by maintaining a normal hemoglobin, the anemia may be corrected, the bone marrow depressed, and ultimately the peripheral blood will contain predominantly normal red blood cells. In this way, it is believed that the risk of surgery may be diminished. The same procedure has been suggested for the treatment of patients with intractable leg ulcers. The possibility of considering this treatment in the last trimester of pregnancy for patients with sickle cell anemia and sickle cell variants is also mentioned.

Acknowledgments

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SUMMARIO IN INTERLINGUA

Le presentia de anemia a cellulas falciforme rende le tractamento de patientes de chirurgia plus complicate. Illo rende le operation chirurgic plus riscose. Es describite un methodo de preparar patientes con anemia a cellulas falciforme pro le operation chirurgic per medio de transfusiones de paccate erythrocytos. Es presentate le reporto de un caso pro demonstrar certes del specific problemas inherente in iste situation.

Le signos e le symptomas in patientes con anemia a cellulas falciforme es producite per le anemia e in plus per occlusive phenomenos vascular que es secundari al falciformantia del erythrocytos. Le causa fundamental es probabilemente un inherente anormalitate in le erythrocytos. Un reducite tension oxygenic, un abassamento del pH, e un augmento del osmolaritate pote promover le tendentia falciformative, e le resultato pote esser un circulo vitiose de erythrostase. Le conditiones presente durante le intervention chirurgic e durante le periodo postoperatori pote precipitar le processo falciformatori. Per effectuar repetite transfusiones de paccate erythrocytos normal e per mantener normalitate de hemoglobina, on pote succeder a corriger le anemia e a producer un depression del medulla ossee. Le effecto final de isto esserea que le sanguine contine predominantemente erythrocytos de conformation normal. Il es plausibile creder que le riscos del intervention chirurgic es reducite per iste mesuras. Le mesme mesuras es recommendate quando on ha a facer con patientes suffrente de intractabile ulceres de gamba. Es etiam a mentionar le possibilitate de considerar iste tractamento in le ultime trimestre de pregnantia in le caso de patientes con anemia a cellulus falciforme o con variantes del phenomeno falciformatori.

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ACUTE NONSPECIFIC PERICARDITIS WITH CARDIAC TAMPONADE: A FATAL CASE ASSOCIATED WITH ANTICOAGULANT THERAPY *

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THE prognosis for ultimate recovery in acute nonspecific pericarditis is generally considered to be excellent. In the literature at the present time there is a total of only five reported deaths associated with the disease.[1, 2, 3, 4, 5] These have occurred in a variety of clinical situations and were reviewed by Price and Hutchison in 1956.[5] Still more uncommon is the occurrence of massive intrapericardial hemorrhage with cardiac tamponade during the course of the disease; three such instances have been reported.[1, 4, 5] One case, reported by McCord and Taguchi,[1] received anticoagulation therapy for a presumptive diagnosis of

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myocardial infarction but died with cardiac tamponade on the fifteenth hospital day. The present report is the second known case of such sequence, and is reviewed to emphasize the occurrence of fatal intrapericardial hemorrhage in nonspecific pericarditis while on anticoagulant therapy.

Case Report

Present Illness: The patient was a 76 year old Negro female admitted to the Bryn Mawr Hospital in July, 1956, with a chief complaint of severe substernal chest pain radiating to the back and occipital region of approximately two hours' duration.

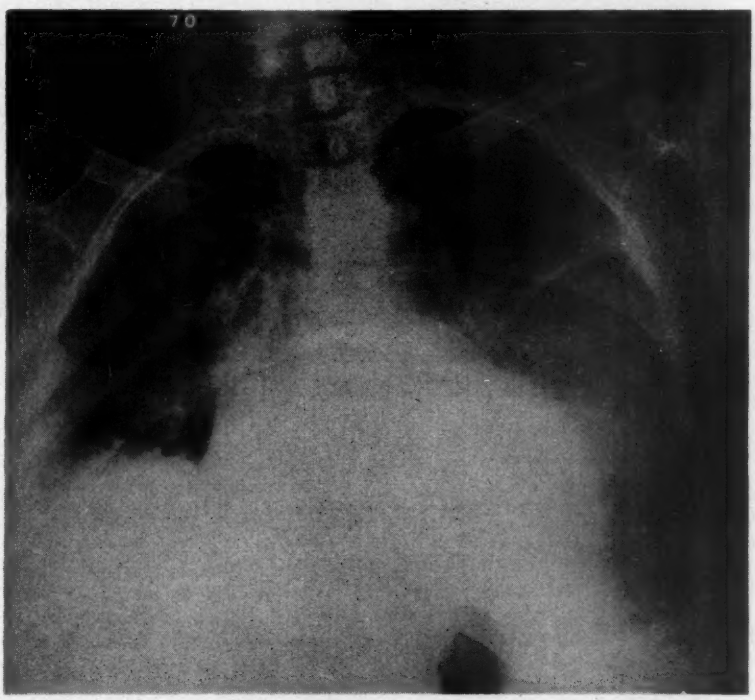

Fig. 1. Chest x-ray one week after admission.

The pain was rather sudden in onset and persistent, and the patient was forced to sit down because of associated weakness and sweating. She was not relieved after a period of rest and within one hour was seen by her local physician, who administered a hypodermic injection of morphine sulfate.

Past History: The patient had always had fatty food intolerance. A cholecystostomy and removal of calculi were performed in this hospital in 1947. During that admission she had a postoperative right pleural effusion and thrombophlebitis. A high femoral ligation was performed, and the patient was discharged improved, without further sequelae. Examination of the heart at that time was not remarkable except for occasional ventricular extrasystoles. An electrocardiogram was within

normal limits in 1944 and again in 1947. There was no past history of diabetes, renal disease, hypertension, angina pectoris or other cardiac disease.

Physical Examination: On admission, the temperature was 98° F.; pulse, 80/min.; respiration, 24/min.; blood pressure, 138/64 mm. Hg. The patient was an obese elderly Negro female, somewhat dyspneic in bed but without apparent cyanosis. She

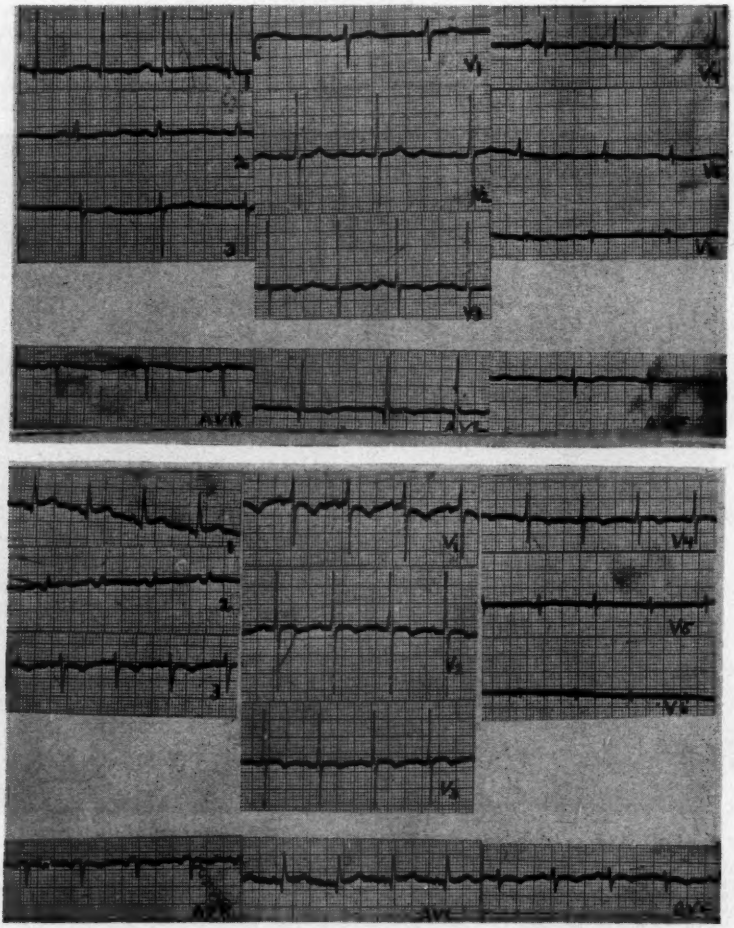

FIG. 2. *A.* Electrocardiogram on admission showing low T waves in all leads. *B.* Electrocardiogram one week later showing deeper T wave inversion.

appeared to be in moderately acute distress, complaining of pain over the precordium and in the region of the cardiac apex. Examination of the head and neck was not remarkable. The lungs were clear except for occasional scattered râles at the bases. The cardiac impulse was palpated in the sixth interspace just outside the left midclavicular line. Heart sounds were normal, with a regular sinus rhythm. No

friction rub or murmurs were noted. The abdomen was soft and no organs were palpated. A 1 plus pretibial edema was noted over the legs.

Laboratory Data: On admission the hemoglobin was 12.6 gm.; red blood count, 3,959,000; hematocrit, 37.0. The white blood count was 7,700, with 81% neutrophils, 15% lymphocytes, 2% monocytes and 2% eosinophils. Erythrocyte sedimentation rate was 27 mm./hr. (Cutler). Urinalysis was not remarkable. Blood chemical tests, including serum bilirubin, fasting blood sugar, blood urea nitrogen and prothrombin time, were within normal limits. Chest x-ray revealed patchy atelectasis in both lower lobes, with a slight left pleural effusion. A repeat chest film one week after admission showed some increase in left pleural effusion and left lower lobe atelectasis. There was increased widening of the base of the heart, thought to be related to a tortuous aorta or aortic aneurysm (figure 1). No mention of pericardial effusion was made. Serial electrocardiograms from the time of the patient's admission showed "abnormal tracings in keeping with left ventricular enlargement and myocardial damage." The changes were those of low, flattened and occasional inverted T-waves in all leads, with a tendency to deeper inversion after the first week of hospitalization (figure 2 A and B).

Hospital Course: On the day after admission the patient's temperature was elevated to 100° F. She was considered to have a probable acute myocardial infarction because of the chest pain, equivocal electrocardiogram and elevated erythrocyte sedimentation rate, and was treated with penicillin and Dicumarol. During the next 24 hours right calf tenderness was noted, and a possible diagnosis of thrombophlebitis and pulmonary embolism was entertained. During the first week of hospitalization the patient had occasional spikes of temperature to 100.5° F. Her chest pain persisted noticeably in the region of the cardiac apex despite rest and sedation. She complained from time to time of nausea and gaseous eructations, and in view of the past history, recurrent gall-bladder disease could not be excluded. Repeated physical examinations of the heart failed to reveal any significant abnormalities. The total white blood count remained normal, with a slightly elevated mature neutrophilic differential in the range of 80%.

On the fourteenth hospital day the patient suddenly developed a state of clinical shock, with profuse sweating and several bouts of vomiting. At that time the blood pressure was 78/50 mm. Hg and the pulse 104. The heart sounds were described as distant in quality. The hemoglobin was 10.5 gm.; hematocrit, 35.5%; white blood count, 19,200, with 92% neutrophils. After approximately two hours her condition improved slightly and the blood pressure rose to 100–80/80–60 mm. Hg. It was also noted on the same day that the prothrombin time was 10% of normal activity, whereas it had been maintained with daily checks in the range of 20 to 25% of normal. There was no external evidence of bleeding. The patient remained in a state of borderline shock, with a fall in urinary output for 14 hours, and died quietly the following day. It was postulated, to explain the patient's clinical state, that a dissecting aneurysm had occurred, although there was no increase in chest pain during this period. A definite clinical diagnosis was not established.

Autopsy Findings: At postmortem examination the significant findings were limited to the chest. There was a left pleural effusion of 1,000 c.c., consisting of straw-colored fluid, with old fibrous adhesions on the pleura. The pericardial sac was distended up to 16 cm. in diameter and the wall thickened up to 0.8 cm.; it contained 700 c.c. of blood and soft clots. The entire inner lining was covered by hemorrhagic fibrinous and fibrous tissue with firm focal adhesions to the epicardium. The heart weighed 550 gm. and was diffusely enlarged. The epicardium was thickened up to 1.0 cm. with gray fibrinous deposits and blood clots. A large amount of grossly normal underlying epicardial fat was identified on all surfaces of the heart. The auricles were normal in size, and no thrombi were present in the appendages. The

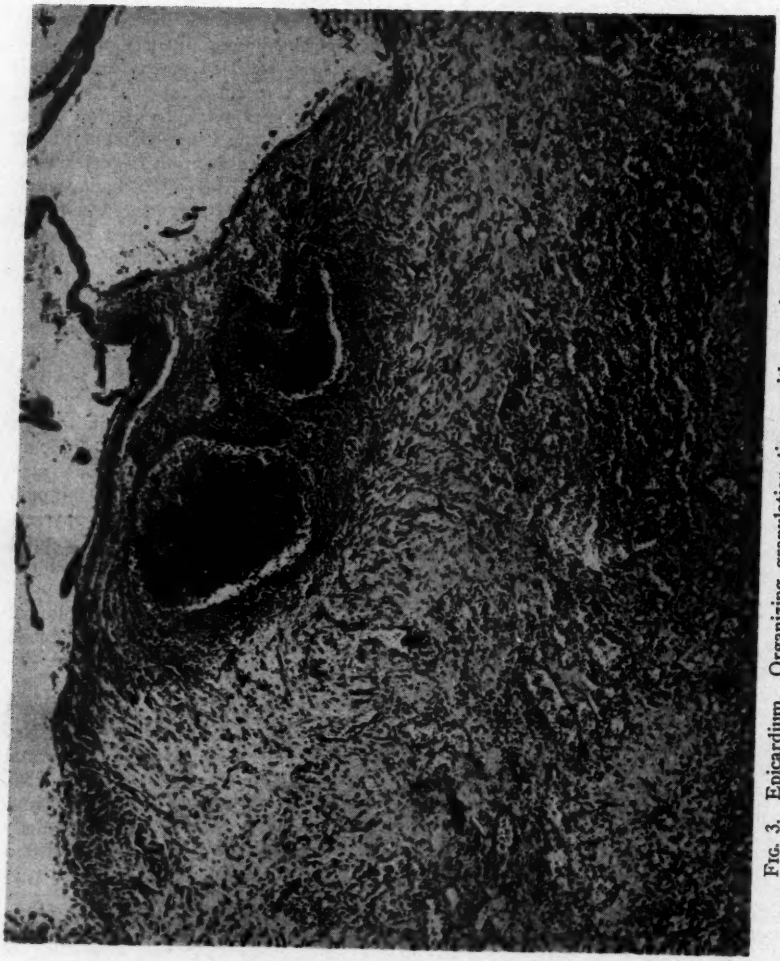

FIG. 3. Epicardium. Organizing granulation tissue with prominently dilated vascular channels. H. & E. × 200.

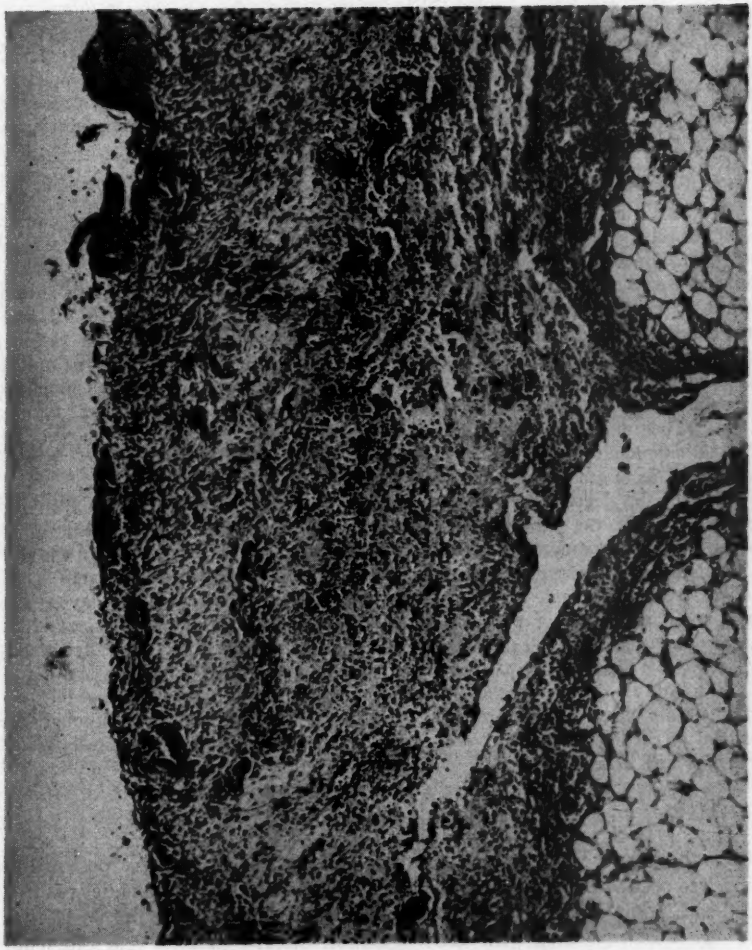

FIG. 4. Epicardium. Sharply demarcated zone of inflammation and fibrous reaction. H. & E. × 200.

ventricular chambers were dilated. The endocardial surfaces were smooth and glistening. All valves appeared to be normal, and there were no abnormalities in size or configuration. The myocardium was homogeneous and dark red throughout, without softening or discoloration. The coronary arteries were focally sclerotic but patent. The base and arch of the aorta were moderately dilated, tortuous and atheromatous, but no aneurysm or dissecting hemorrhage was present.

The right lung weighed 525 gm. and the left lung, 375 gm. The upper lobes bilaterally were moist and subcrepitant. The left lower lobe was almost completely atelectatic and was dark red in appearance. The lungs showed no evidence of pneumonic consolidation or infarction. The trachea, bronchi and major pulmonary vessels were grossly normal. In the abdomen there was moderate fibrosis at the bed of the liver and surrounding the gall-bladder; no calculi were present in the gall-bladder, and the extrahepatic bile ducts were patent and normal in size. The liver, spleen, pancreas and adrenal glands were within normal limits. The right kidney showed focal cortical scarring of chronic pyelonephritis. The remaining organs showed congestion and atrophic changes only.

On microscopic examination the pericardial and epicardial surfaces of the heart were lined by exuberant organizing fibrinous deposits, with marked increased vascularity, congestion and recent bleeding. Other areas showed pronounced cellular fibrous reaction and capillary endothelial proliferation. A dense, sharply delimited band of inflammatory cells consisting of lymphocytes, plasma cells and small numbers of neutrophils and eosinophils was present just beneath the epicardial surface (figures 3 and 4). The underlying epicardial fat and the entire myocardium showed no evidence of inflammation, fibrous reaction or vascular damage. The lungs showed congestion and focal atelectasis only.

In view of the degree of fibrous organization and capillary proliferation on the surface of the heart, the patient's pericardial process must have been present for at least seven to 10 days prior to her death. The dramatic, shocklike episode on the day before death appeared to be related to the sudden onset of intrapericardial hemorrhage. The fall of 2.0 gm./100 ml. in the patient's hemoglobin during the last day of life reflects a total blood loss of approximately 600 ml., using an estimated total blood volume of the patient as 4,000 ml. This loss represents almost exactly the accumulation of pericardial blood. The patient's anticoagulant therapy no doubt played a major contributing role in the development of the hemopericardium, since the bleeding occurred at a time when the prothrombin activity was 10% of normal. Although the patient died of cardiac tamponade, it is very doubtful that a pericardiocentesis would have been of any benefit.

Discussion

Although rare cases of chronic recurring disease and constrictive pericarditis are known to occur following nonspecific pericarditis, cardiac tamponade was first reported as a complication of the disease in 1951.[1] In that case the pericardial hemorrhage was associated with anticoagulation therapy in a 52 year old white male who died suddenly on the sixteenth hospital day. The patient had received heparin and Dicumarol because of a suspected diagnosis of myocardial infarction. The prothrombin activity was maintained at about 25% of normal for 14 days. On one occasion it fell to 6.5%, but this is not clearly correlated with the patient's death. Autopsy confirmed a diffuse fibrinous pericarditis with hemopericardium; a myocardial infarction was not present. Two other cases of spontaneous cardiac tamponade have been reported in nonspecific pericarditis unassociated with any form of anticoagulant therapy. One of these was reported in

1952 by Pomerance et al.[4] in a patient suspected of having acute pancreatitis who died six hours after hospital admission. An extensive fibrinous pericarditis and intrapericardial hemorrhage were found at postmortem examination. The second case, reported by Price et al.[5] in 1956, was that of a young man who had been ill for one month at home and died one week after hospitalization. Pericardial taps during life yielded 400 c.c. and 550 c.c. of bloody fluid on two occasions. Autopsy disclosed a hemopericardium and nonspecific fibrinous pericarditis.

The clinical course of acute nonspecific pericarditis is frequently confused with that of acute coronary thrombosis, despite apparent differences reported by numerous authors.[6, 7, 8] The finer points in symptomatology, physical examination, laboratory studies and electrocardiographic findings have all been adequately emphasized and are beyond the scope of this report. Goyette in 1953[9] reviewed a series of 28 cases of nonspecific pericarditis in which 22 were initially diagnosed as having acute myocardial infarctions. In that series no deaths occurred, although the course of the disease was quite variable from patient to patient. In 1944 Weinstein [10] reported 10 cases of atypical coronary disease in young soldiers. This material was reviewed in 1948 by Logue and Wendkos,[11] who felt on the basis of a closer analysis of the clinical and electrocardiographic findings, that some of these were probably instances of nonspecific pericarditis. These authors reported 17 additional cases of acute pericarditis, six of whom had initial incorrect diagnoses of coronary occlusions. Porter et al.[12] reviewed 219 patients with acute pericarditis due to varying etiologic factors. A diagnosis of angina pectoris or coronary occlusion was tentatively made in eight, and was mentioned as a possibility in 100% of cases. Numerous other similar studies have been reported in the literature. Because of the great dissimilarity in the immediate and ultimate prognosis, and in the light of present-day anticoagulant therapy for myocardial infarction, clinical differentiation is fundamentally important and cannot be overemphasized.

The occurrence of hemopericardium in nonspecific pericarditis is related to the period of very extensive capillary proliferation and early organization of the fibrinous exudate on the epicardial and pericardial surfaces. As a rule this takes place between the first and second week, and is usually at a maximum about the tenth to the fourteenth day after the initiation of the fibrinous process. It is easy to understand, then, why intrapericardial hemorrhage might occur more frequently in the presence of an anticoagulant, at a time when the entire surface of the heart is transformed into an exuberant proliferation of granulation tissue and capillary vessels. Usually pericardial effusion in these patients is clear or only slightly blood-tinged prior to the end of the first week of illness, and thereafter takes on a more hemorrhagic character. Nathan and Dathe [13] reviewed eight cases of acute pericarditis associated with upper respiratory infections, in five of whom pericardiocentesis was performed. The fluid was hemorrhagic in four and clear in one. Analysis of these figures shows that the duration of the illness in the case with clear fluid was two days, while in all others the history was over one week in duration. Price et al.[5] analyzed a series of 20 separately reported cases, of which 50% yielded bloody pericardial fluid. These instances of hemorrhagic effusions occurred after the tenth day of illness, whereas in cases of shorter duration serous fluid was observed.

Summary

This report presents the second known case of cardiac tamponade in nonspecific pericarditis associated with anticoagulant therapy. A total of four cases of hemopericardium in the course of the disease have appeared in the literature, two unassociated with the use of anticoagulant drugs. While cardiac tamponade may be more common in secondary forms of pericarditis, it is decidedly uncommon in the idiopathic or primary form of benign pericarditis. The importance of differential diagnosis between myocardial infarction and nonspecific pericarditis is stressed. The use of anticoagulants is contraindicated in the latter group of patients.

Summario in Interlingua

Iste reporto presenta le secunde cognoscite exemplo de mortal hemorrhagia pericardial associate con therapia anticoagulante in le curso de un acute pericarditis non-specific. Le caso es illo de un negressa de 76 annos de etate qui recipeva dicumarol in doses therapeutic pro un suspecte infarcimento myocardial. Illa moriva subitemente le dece-quarte die de hospitalisation in le presentia de tamponage cardiac. Le necropsia revelava un hematopericardio de 700 cm^3 de sanguine e coagulos molle, con pericarditis fibrinose organisante e hemorrhagic diffuse. Nulle signo de un subjacente morbo myocardial esseva trovate. Le prime tal caso, reportate per McCord e Taguchi in 1951, esseva simile in tanto que le patiente moriva de tamponage le dece-quinte die. Il es ben cognoscite que le curso clinic de acute pericarditis non-specific es facile a confunder con le curso clinic de acute infarcimento myocardial. Il es impossibile exaggerar le importantia del differentiation inter le duo, proque le uso de anticoagulantes es contraindicate in pericarditis benigne. Hemorrhagia occurre in iste patientes a un tempore quando le superficies epi- e pericardial es coperite de juvene capillares proliferante e fibroblastic histo conjunctive. Iste supposition es reinfortiate per reportate pericardiocenteses in casos non-mortal de pericarditis. In quasi omne tal casos le fluido esseva de character serose ante le decime die del maladia e sanguinose o hemorrhagic post ille tempore. Per consequente le uso superimponite de anticoagulantes resulta in le obvie complication de hematopericardio.

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HYPOKALEMIC ALKALOSIS WITH AN UNUSUAL BLOOD CHLORIDE LEVEL *

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It is the purpose of this case presentation to emphasize the importance of metabolic alkalosis, to demonstrate such a case precipitated and augmented by an illness frequently encountered in clinical practice, and to report an electrolyte abnormality of unusual severity with survival.

Case Report

A 38 year old white female was admitted to Philadelphia General Hospital, on the service of Dr. Boles, on May 20, 1955, with grand mal seizures of 12 hours' duration. Past history revealed a hospitalization six months previously for cholecystitis and cholelithiasis, for which she had refused surgery. Following discharge the patient, a chronic alcoholic, became engaged in constant bouts of drinking. For one week prior to admission her sole intake consisted of alcoholic beverages. Vomiting and pain in the epigastrium and right upper quadrant followed with increasing severity. On the day of admission the patient became incoherent and lethargic, had five grand mal seizures and lapsed into coma.

Physical examination disclosed a dehydrated and hyperirritable patient who responded to painful stimulation. Vital signs indicated a blood pressure of 90/60 mm. of Hg; temperature, 101° F. (rectal); pulse, 100; respirations, 22 and normal. There was no cyanosis. Dental hygiene was poor. Tenderness was present in the epigastrium and right upper quadrant. Bilateral Babinski's signs and hyperactive reflexes were elicited. The remainder of the examination was within normal limits.

Laboratory data revealed the following derangements: CO_2 combining power, 44.1 mEq./L.; chlorides, 41 mEq./L.; sodium, 112 mEq./L.; potassium, 1.7 mEq./L.; blood urea nitrogen, 50 mg./100 ml. Urinalysis showed acetonuria and 15 to 20 white blood cells; *Escherichia coli* was cultured. Spinal fluid examination, liver function studies, blood count and blood sugar were within normal limits. An x-ray of the chest was normal. An electro-encephalogram was interpreted as increased cortical excitability which could have been due to an intoxication or metabolic disturbance. An electrocardiogram taken prior to therapy showed changes consistent with hypocalcemia (figure 1). The results of repeated laboratory examinations appear in table 1.

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Upon admission a futile attempt was made to control the convulsions with sodium amytal. Further therapy was directed primarily toward correction of the electrolyte imbalance. During the first 12 hours, 2,300 c.c. of fluid were given intravenously; this consisted of 300 c.c. 3% sodium chloride, 500 c.c. 5% dextrose in saline, and the

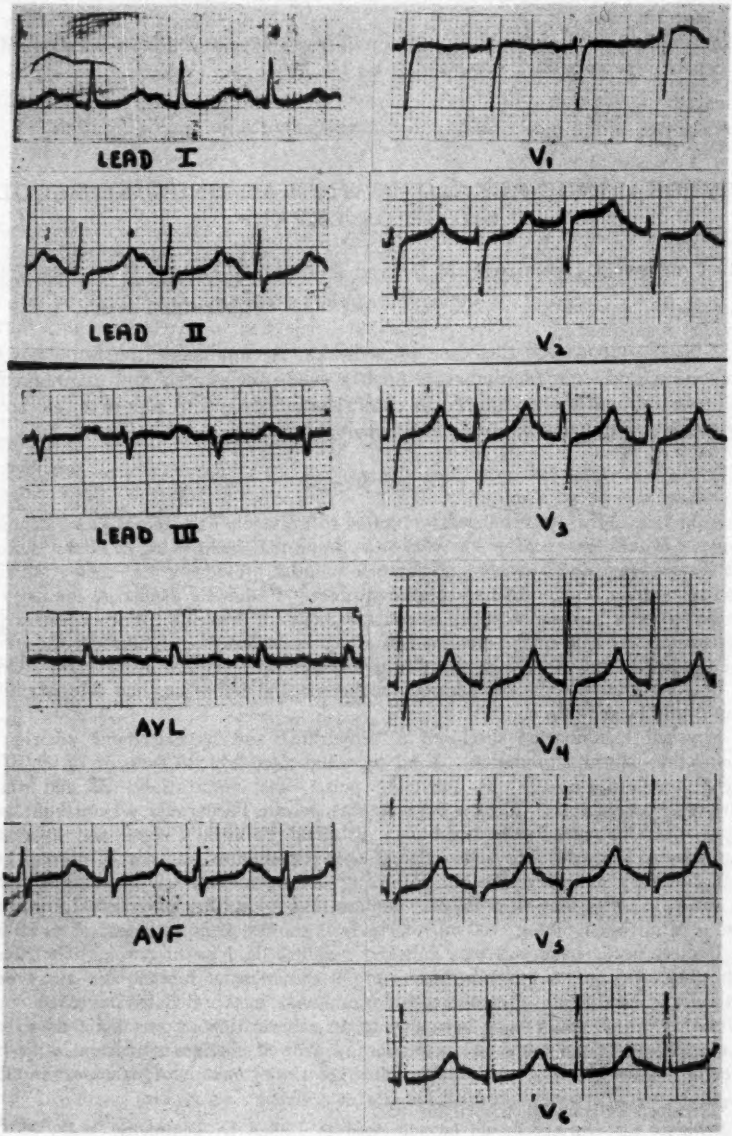

FIG. 1. Electrocardiogram taken prior to treatment showing prolongation of QT interval which is consistent with hypocalcemia.

remainder dextrose in water. Large doses of vitamins and a total of 4 gm. of potassium chloride and 2 gm. of calcium gluconate was added to the infusions. Immediately following this the patient became alert and ambulatory. Abdominal tenderness diminished, Babinski's signs disappeared and hyperactivity of deep tendon reflexes diminished over the next few days. The patient was continued on intramuscular vitamins, 2 gm. of potassium chloride and 6 gm. of ammonium chloride daily by the oral route. After one week of therapy the serum electrolytes were still abnormal, but a definite trend toward normal concentrations was apparent (table 1).

A review of the literature fails to show a chloride level as low as 41 mEq./L. with survival. Severe hypochloremia with values of 76 mEq./L. has been reported.[9] One of us (L. D. D.) has noted chloride levels of 55 mEq./L. in uremic patients treated with hypertonic sodium lactate.[30] At this low concentration patients were lethargic but demonstrated no gross neurologic abnormalities. It is interesting to note that after 12 hours of therapy the chloride concentration rose to only 64 mEq./L. but our patient became subjectively asymptomatic. Such a severe hypochloremia must be followed by hypokalemia, although the patient's poor intake undoubtedly played a part in the low potassium concentration.

TABLE 1

Serum Electrolyte Determinations before Therapy (May 20), and the Trend toward Normal Concentrations after Therapy

Date	mEq./L.					mg./100 ml.			Gm./100 ml.	
	Na	K	Cl	CO_2	Δ	BUN	Ca	P	Total Proteins	A/G Ratio
May 20	112	1.7	41	44.1	28.6	50				
May 21	122	2.2	64	42.3	17.9					
May 22	123	2.6	74.9	36.5	14.2		8.6		8.2	4.3/3.9
May 26							10.4	2.7	7.2	4.3/2.9
May 27	123	3.3	92.1	22.5	11.7	9				

$\Delta = (Na + K) - (CO_2 + Cl)$ or undetermined anions.

A deficit in the anion column is apparent (table 1). Organic acid ions such as lactate, acetyl acetate and beta-hydroxybutyric acid should be considered as the major constituents of the undetermined anions, lactate being increased in the convulsive state and the other acids as a result of starvation.

COMMENT

The causes for metabolic alkalosis are many. They may include the direct loss of fixed anion (Cl) from gastric fluid during vomiting or suction,[1-4] congenital diarrheal loss of chloride,[5, 6] retention of fixed cation (sodium) following ingestion of alkali or antacids,[9] excess of chloride over sodium excretion during mercurial diuresis,[7] continued therapy in chronic uremia with hypertonic sodium lactate,[8] a combination of disproportionate chloride excretion and transfer of H^+ and Na^+ into the extracellular space in potassium deficiency,[10, 11] and hypersecretion of mineralocorticoids.[29]

The imbibing of alcohol does not per se produce an alkalosis. Urine flow is initially increased. A water diuresis exists, since solute excretion is minimal and extracellular acidosis may follow with increased excretion of titratable acid and ammonia.[12, 13, 22, 23] However, other investigators have demonstrated a

hypochloremia as a result of excessive water and low salt intake combined with excessive chloride loss in the urine and sweat.[24]

It is felt that vomiting in our patient was induced by alcoholic irritation of the gastrointestinal tract and was further aggravated by a diseased gall-bladder. Metabolic alkalosis ensued by loss of chloride and potassium and, to a lesser extent, sodium. In such instances, the excess sodium remains to unite with the increased amount of carbonic acid resulting from catabolism; subsequently, the bicarbonate level rises. Such an elevation of bicarbonate level predisposes to further alterations in tissue electrolytes.[21, 26]

The fundamental factor responsible for the intracellular alterations is a change in pH of the extracellular space. This postulation is based on the finding in hypokalemic alkalosis of an increased intracellular sodium usually equaling two thirds of the intracellular potassium decrease, thus lending itself to the hypothesis that upon administration of potassium this extracellular ion is exchanged for hydrogen ion in the cell. Therefore, in potassium deficiency per se, the extracellular alkalosis is accompanied by an intracellular acidosis.[16, 17, 19] Potassium deficiency is produced by hypochloremic alkalosis, the degree of deficiency being directly proportional to the loss of chloride.[14, 15] Therefore, the presence of metabolic alkalosis presents evidence of intracellular potassium depletion.[28]

Alterations in the central nervous system in this patient may be attributed to changes in the blood pH rather than to alcoholism. With the latter, neurologic signs disappear slowly.[25] Alkalosis decreases the proportion of ionized calcium and increases neuromuscular irritability. In this mechanism, the rate of change in the level of serum calcium is of paramount importance. A sudden reduction is more apt to produce tetany than is a similar degree of reduction occurring over a period of time.[27] It has long been recognized that calcium and potassium are physiologic antagonists in neuromuscular activity. From this it would seem that a low concentration of potassium tends to limit the severity of hypocalcemic tetany.[19, 27] For that reason, in the presence of hypocalcemia and hypokalemia, simultaneous administration of calcium and potassium is recommended.

Howard [20] emphasizes the slowness in response in the serum chloride and bicarbonate, each taking five days before it starts toward normal levels, and 10 days before it actually is normal. Potassium reaches a stable normal concentration by the ninth day. The addition of ammonium chloride and potassium to our patient's diet undoubtedly hastened the reversal toward normal of the serum electrolytes. It has been shown that the use of sodium chloride alone aggravates a hypochloremic alkalosis.[3, 4, 18]

Summary

A case is presented of metabolic alkalosis with an unusually low blood chloride level, with survival. It is felt that the precipitating agent was alcohol, which caused irritation of the gastrointestinal tract and excited an already diseased gall-bladder, and thus led to vomiting, inadequate intake, and starvation.

Some concepts concerning alterations in body fluids and therapy for hypokalemic alkalosis are discussed.

ACKNOWLEDGMENT

We wish to thank Dr. John Reinhold for his technical advice in preparing this paper.

SUMMARIO IN INTERLINGUA

Le objectivo del presente reporto es sublinear le importantia de alcalosis metabolic, demonstrar un caso de illo precipitate e augmentate per un pre-existente morbo del vesica biliari, e publicar un anormalitate electrolytic de inusual grados de severitate in que le patiente superviveva.

Un alcoholica de 38 annos de etate e de racia blanc esseva admittite al hospital con attaccos de haut mal. Durante un septimana ante su hospitalisation, su ingestion total habeva consistite de bibitas alcoholic. Vomito e dolores abdominal sequeva con grados crescente de severitate. Le examine physic monstrava un patiente in stato comatose qui esseva etiam dishydratate e hyperirritabile. Le constatationes positive includeva sensibilitate sub pression in le epigastrio e le quadrante dextero-superior, signos de Babinski bilateral, e reflexos hyperactive.

Le datos laboratorial revelava le sequente disordines: Potentia combinatori pro CO_2, 44,1 mEq/L; chloruros, 41 mEq/L; natrium, 112 mEq/L; kalium, 1,7 mEq/L; e nitrogeno de urea sanguinee, 50 mg/100 ml. Le urinanalyse monstrava acetonuria e un numeration leucocytic de 15 a 20. *Escherichia coli* esseva culturate. Un electro-encephalogramma supportava le interpretation de augmentate excitabilitate cortical, causate per intoxication o per disturbation metabolic. Le electrocardiogramma monstrava alterationes compatibile con hypocalcemia.

Le therapia visava primarimente a corriger le imbalancia electrolytic. Esseva date 300 cm^3 de chloruro de natrium de 3%, 500 cm^3 de 5% de dextrosa in solution salin, fluido additional exclusivemente in le forma de dextrosa in aqua, grande doses de vitaminas, e un total de 4 g de chloruro de kalium e de 2 g de gluconato de calcium —omnes per via intravenose. Dece-duo horas plus tarde le patiente esseva alerte e ambulatori. Le dolores abdominal habeva recedite. Le signos de Babinski habeva disparite. Le hyperactivitate del reflexos del tendines profunde habeva decrescite. Le patiente continuava reciper chloruro de kalium e chloruro de ammonium in doses diurne per via oral. Un septimana plus tarde le electrolytos del sero esseva ancora anormal, sed un definite tendentia in le direction de concentrationes normal esseva apparente. Un revista del litteratura ha producite nulle altere caso de un nivello de chloruro de non plus que 41 mEq/L con superviventia del patiente.

Es discutite certe conceptos relative a alterationes del fluidos corporee e al therapia in casos de alcalosis hypokalemic.

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SPINAL CORD COMPRESSION DUE TO EXTRAMEDULLARY HEMATOPOIESIS *

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Extramedullary hematopoiesis, or myeloid metaplasia, is a frequently encountered condition, occurring usually in association with certain types of anemia. It is particularly prone to occur with anemia due to myelophthisis or myelosclerosis, and is usually thought of as a compensatory mechanism whereby extramedullary tissue attempts to compensate for a deficiency of the marrow. However, extramedullary hematopoiesis is found often in autopsy material from cases in which there is no detectable bone marrow deficiency. Cholesterolemia and arteriosclerosis (experimentally), and various toxins and infections, are also known to be capable of initiating extramedullary hematopoiesis.[9, 12] Regardless of the cause or causes, in our experience, the most common sites of extramedullary hematopoiesis are the liver, spleen, lymph nodes and adrenal glands. (Table 1 lists sites of blood production occurring normally in the embyro or newborn.) We have recently encountered a case of myelosclerosis in which extramedullary hematopoiesis occurred in the vertebral canal. For reasons to be discussed, we feel that this should be reported.

Case Report

A 60 year old white male was admitted on August 31, 1954, with complaints of a 60 pound weight loss and increasing weakness over a two year period.

Eight months prior to admission a diagnosis of myelophthisic anemia had been made on the basis of bone marrow and peripheral blood studies. A nonfunctioning right kidney, destroyed by pyelonephritis, was removed at another hospital, and a few days after operation the patient noted rather sudden onset of marked weakness and numbness of the legs and was soon unable to walk. There was no pain and no sphincter dysfunction. The weakness improved somewhat, but numbness of the soles of his feet persisted. He began to have moderate ankle edema and exertional dyspnea shortly before admission to our hospital. There was no history of exposure to any of the commonly known bone marrow depressants.

Examination: The patient was a chronically ill, very pale white male. The blood pressure was 110/80 mm. of Hg; pulse rate, 108. The liver and spleen were moderately enlarged. No lymphadenopathy was noted. There was mild ankle edema. There was no tenderness along the vertebral column. The cranial nerves were normal, but there were moderate atrophy and weakness of all muscle groups of both lower limbs. There was marked ataxia during performance of the "heel-knee-toe" test. Vibratory sense was absent below the thoracic cage, while pain, touch and temperature senses were intact. Deep tendon reflexes were present, equal and considered normal, as were the superficial reflexes. There were no pathologic toe signs.

Laboratory: Bone marrow aspiration and trephine again revealed extensive sclerosis with no hematopoietic cells. Electro-encephalogram, proctoscopy, complete

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gastrointestinal series, skull, lung and spine roentgenograms, Kolmer's test and serum acid phosphatase levels were all normal. Electrocardiogram revealed a nodal rhythm. The hemoglobin on admission was 4.5 gm., but after transfusions rose to as high as 11.0 gm., although usually fluctuating between 6.0 and 9.0 gm. The white blood counts ranged between 1,650 and 9,800 per cubic millimeter, more often being less than 5,000, with 30 to 40% segmented neutrophils, 15 to 30% stab forms, 2 to 4% metamyelocytes, 1 to 4% myelocytes, and 2 to 14% blast forms. Nucleated red cells were occasionally seen, and the platelets were reduced in number.

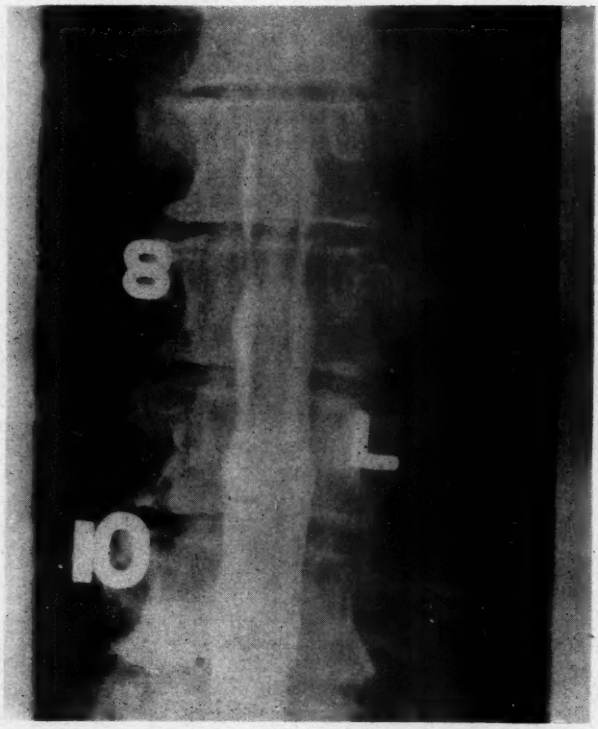

FIG. 1. Preoperative myelogram, showing block at lower margin of eighth thoracic vertebra.

Hospital course: The neurology consultant thought that the findings represented a lower motor neurone lesion with posterior column involvement. He thought that subacute combined degeneration did not satisfactorily explain the findings and recommended myelography and neurosurgical evaluation.

Lumbar spinal puncture was done and an initial pressure of 140 mm. was found, with no rise on bilateral jugular compression. The fluid was clear and colorless. Spinal fluid examination revealed a protein of 184 mg.%, a 5555432100 gold curve, and a negative Kolmer's test. Myelography with Pantopaque revealed a block at about the level of the eighth thoracic vertebra (figure 1).

Laminectomy from the eighth to the tenth thoracic vertebrae was done under local anesthesia, and a mass composed of soft, friable, purplish tissue was found in

the extradural space. Tumor biopsy and frozen section study revealed hematopoietic tissue. The tumor was loosely attached to adjacent structures and, as gauged by suction exploration, appeared to cover the posterior surface of the dura from the level of the twelfth up to at least the fifth thoracic vertebra (figure 2). Most of the tissue was removed up to the latter level with a suction tip. If the tumor was an extension from hematopoietic tissue within the dura or vertebral marrow, it was not apparent within the visible part of the operative area.

There was little improvement in the neurologic changes or muscle strength following surgery. Cerebrospinal fluid dynamics two months after surgery again revealed a block. For this reason, radiation therapy was administered to the middle and upper thoracic spine. Ambulation was gradually accomplished, but there was no improvement in the neurologic findings or muscle strength. Two or three trans-

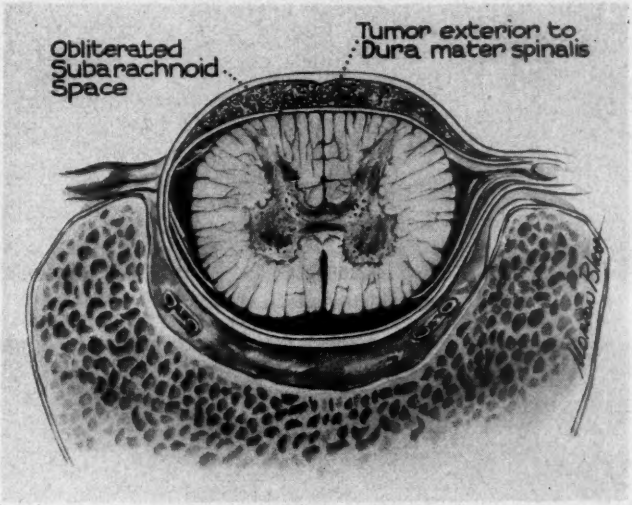

FIG. 2. Artist's conception of cross section of eighth thoracic vertebra through inferior margin of pedicle; shows approximate location and extent of tumor.

fusions of red cell mass were required each month to maintain the hemoglobin level above 9.0 gm. The patient was given cortisone, Meticorten and vitamin B_{12}, but grew progressively weaker and died on December 9, 1955. Permission for autopsy was refused.

Pathology: Gross: The specimen consisted of numerous fragments of tissue, estimated at about 30 in number, and averaging 5 by 2 by 2 mm. in size. All had a similar appearance, were a rather uniformly deep brownish red with hemorrhagic mottling, and were soft and friable.

Microscopic (figures 3 and 4): All the fragments submitted were cellular and consisted of both erythroid and myeloid elements within a delicate, lacelike background. There were also numerous polymorphonuclear neutrophils, and in a few small areas eosinophilic polymorphonuclear cells and myelocytes predominated. Included among these cells were several megakaryocytes. An occasional cell in mitosis was seen. A few fat cells, singly and in small groups, were interspersed among the hematopoietic cells, and there were numerous small and irregular areas of hemorrhage.

Diagnosis: Extramedullary hematopoiesis.

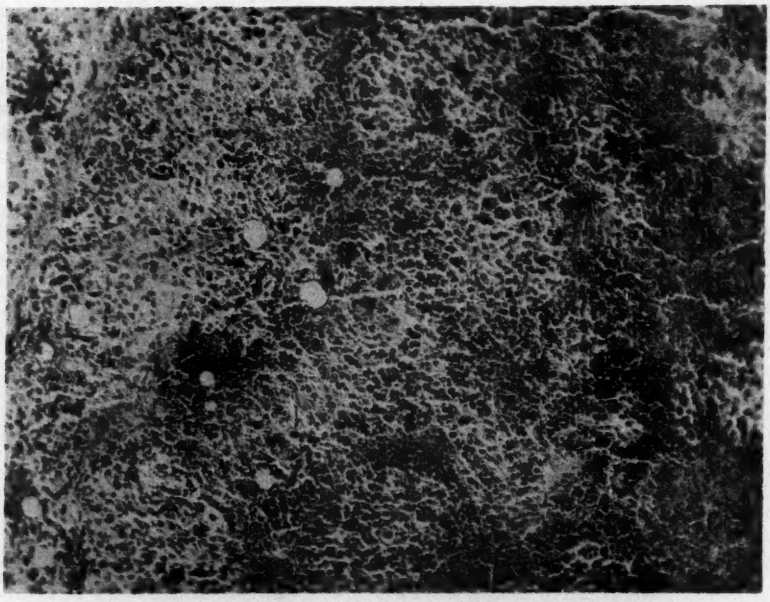

FIG. 3. Representative section of tumor. × 85.

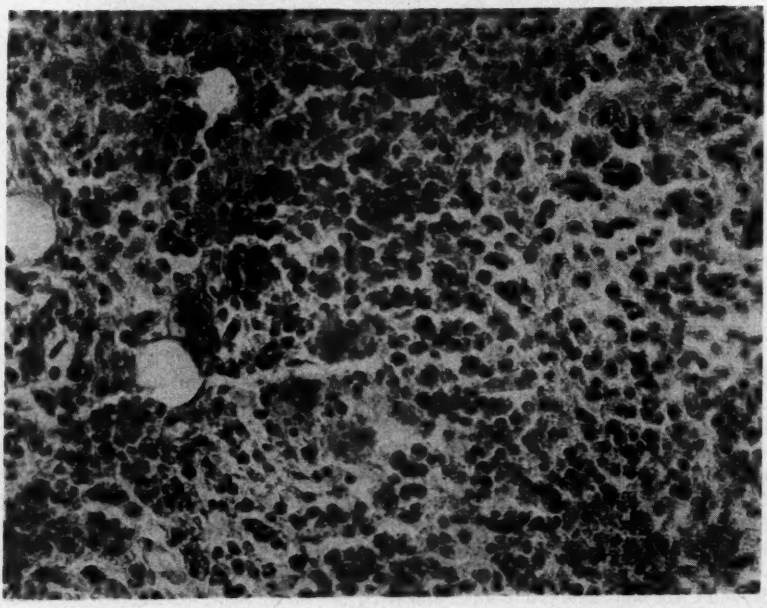

FIG. 4. Center of section in figure 3. Note fat cells and megakaryocytes to left of center. × 270.

Discussion

This case is unusual because of the location of the elements of ectopic blood formation, and also because these elements formed a solid tumor of a size sufficient to cause spinal cord compression. It is probable that the spleen and liver were also involved.

The impressive list of synonyms for this condition adequately supports the impression that considerable controversy exists regarding the exact nature of myelosclerosis. Its differentiation from leukemia may be difficult. Some consider myelosclerosis to be a distinct entity, others feel that it may be caused by a variety of factors. Dameshek [4] has suggested that it may be a stage of a myeloid leukemic state. It is not our intention to enter into this controversy, other than to point out that extramedullary hematopoiesis is rarely, if ever, seen in the adult in sites other than those in which it occurs normally in the fetus (table 1).

Table 1

Sites in Which Extramedullary Hematopoiesis Has Been Described by Others or Seen by Authors

* Spleen
* Liver
* Kidney
* Adrenal
* Heart
* Lymph nodes [3]
* Thymus [3, 6]
* Lungs or pleura [1, 3, 7]
* Kidney pelvis [3, 9]
* Retroperitoneal fat [2, 9, 12]
* Gastrointestinal lymphatics [3, 6]
* Dura mater, cranial [3, 7, 11]
Broad ligament [3]
Breast [3, 5]
Sweat glands of hands and feet [5]
Prostate and epididymis [5]
Dura mater, spinal
† Thoracic duct [10]

* Sites in which hematopoiesis has also been described in embryo or newborn.
† Described in embryo only.

A review of the medical literature of the past 40 years failed to reveal any report of extramedullary hematopoiesis occurring within the vertebral canal. However, we doubt that it occurs as rarely as this fact would suggest, since hematopoietic function does exist in the dura mater of the fetus and this region is not routinely studied at autopsy. We furthermore suggest the possibility that cases similar to ours may have been diagnosed as subacute combined degeneration in the past. Although our review of the literature yielded no case similar to the one reported here, Hu and Cash [8] described two cases of extramedullary hematopoiesis resulting in the formation of an extradural tumor over the brain in 1930. This occurred as a complication of kala-azar, and erosion of the inner table of the skull was produced by marked hyperplasia of the marrow. Brannan [3] reported extramedullary hematopoiesis in the cerebral falx of an infant.

Neurologic symptoms and findings can be associated with anemia per se, or can be caused by the degenerative effects of anemia on the spinal cord (subacute combined degeneration). The purpose of this presentation is to point out that,

should even a suggestion of cord compression arise, study of cerebrospinal fluid dynamics and myelography are indicated. Since cord compression had been present for nine months in this case, it is not surprising that only negligible improvement followed the decompression. Rapid regeneration of the hematopoietic elements may occur and thereby nullify the benefits of operative treatment. The problem of therapy for a condition such as this is magnified by the fact that the tumor presumably serves a useful function, and its removal could result in aggravation of the basic problem—in this case, pancytopenia. Radiation will destroy the hematopoietic elements but must be used judiciously to avoid loss of blood formation in spleen and liver.

Summary

1. A report of an unusual site of ectopic blood formation in a patient with myelosclerosis is presented.

2. Sites in which extramedullary hematopoiesis occurs in disease states are listed, and comparable areas of hematopoiesis described in the fetus or newborn are noted.

3. The importance of awareness of this condition as a clinical entity is stressed. Early investigation by cerebrospinal fluid dynamics and myelography is urged for neurologic syndromes which could conceivably be a result of cord compression by extramedullary hematopoietic tissue.

Summario in Interlingua

Hematopoiese extramedullar es incontrate frequentemente in patientes con anemia myelophthisic. A vices illo es etiam vidite in patientes con detegibile carentia de medulla ossee. Un revista del litteratura del passate 40 annos revela nulle reporto de un affection del canal vertebral per histos hematopoietic.

Es reportate le caso de un masculo caucasian de 60 annos de etate, admittite al hospital a causa de progressive perdita de peso e debilitate general de un duration de duo annos e torpor e debilitate del gambas de un duration de octo menses. Octo menses ante le hospitalisation, un diagnose de anemia myelophthisic habeva essite facite. Le patiente exhibiva moderate hepatosplenomegalia, sever ataxia, e moderate atrophia e debilitate de omne gruppos de musculos gel gambas. Nulle senso vibratori esseva presente infra le cavia thoracic. Trephination de medulla ossee e studios de sanguine peripheric confirmava le diagnose de myelophthisis con pancytopenia.

Le constatationes esseva considerate como indicante un lesion de neurones motori inferior con affection del columna, non satisfactorimente explicabile per subacute degeneration combinate. Studios chimic del fluido cerebrospinal revelava un elevate nivello de proteina. Studios dynamic e myelographic (a Pantopaque) revelava un extense tumor extradural componite de histo hematopoietic, sin sito de origine definitemente apparente. Ablation del plus grande parte del tumor esseva effectuate per medio de suction. Nulle notabile alteration del stato neurologic del patiente se manifestava, e duo menses plus tarde un bloco esseva presente. Radio-therapia esseva administrate al spina thoracic, sed sin apparente beneficio. Le patiente deveniva progressivemente plus debile e moriva 16 menses plus tarde.

Hematopoiese extramedullari es vidite rarmente in adultos in sitos altere que le sitos in que illo occurre normalmente in le feto. Illo ha essite describite como occurrente in le falce cerebral del feto. Il es possibile que su occurrentia in le canal vertebral in statos pathologic non es un raritate, proque le canal vertebral non es

includite routinarimente in le examine necroptic. Casos simile al caso del presente reporto es facile a confunder con subacute degeneration combinate. Ante que on accepta un diagnose de subacute degeneration combinate, omne signo suspecte de compression del medulla spinal debe esser investigate per methodos de dynamica e de myelographia.

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12. Petri, E.: Über Blutzellhende im Fettgewebe des Erwachsenen und ihre Bedeutung für die Nervbildung der weissen und roten Lymphknoten, Virchows Arch. f. path. Anat. **258**: 37–51, 1925.

EDITORIAL

THE ERADICATION OF MALARIA AS AN ENDEMIC DISEASE IN THE UNITED STATES

ALTHOUGH much has been accomplished toward the eradication of malaria from the United States [1, 2, 3] and from some other countries,[4, 5] for the world in general it continues to be a major medical problem. President Eisenhower, in presenting evidence to support his Foreign Aid Bill, "shocked" Congress when on May 27, 1957, he truthfully said that "malaria is *today* the world's foremost health problem." [6] "Malaria still attacks 200,000,000 and kills 2,000,000 people each year throughout the world." Malaria, therefore, still occupies first rank in man's afflictions as a cause of morbidity.

The clinical features and natural history of the malarial fevers, which were endemic in Greece, were well described in the Hippocratic writings (Fourth Century B. C.),[7, 8] and the suggestion was made that these periodic fevers were caused by drinking stagnant marsh water. The Romans, who initiated many important public health measures, advised against erecting buildings on public highways near marshy swampland, "whereby hidden diseases are contracted and there are animals with insidious stings." [9] During the seventeenth century, after the inertia of the Middle Ages was overcome, speculation and interest in malaria developed anew. It was during this period that Peruvian bark (cinchona) was introduced into Europe from South America by the Spaniards (1640) for the treatment of fevers.

Precise knowledge, however, virtually began with the observations of Alphonse Lavaran, a French military surgeon working in Algeria, who in 1880 described the malarial parasites in microscopic preparations of fresh blood of a soldier with the disease. He stated that "Attacks of malaria are produced by the introduction into the blood of parasites which appear in the various forms herewith described. It is because quinine kills these parasites that it cures malaria." Although this report was skeptically

[1] Pampana, E. J., and Russell, P. F.: Malaria: A world problem, Chronicle of the World Health Organization **9**: 33–96, 1955.

[2] Andrews, M. J., et al.: Malaria eradication in the United States, Am. J. Pub. Health and the Nation's Health **40**: 1405, 1950.

[3] Andrews, M. J.: Personal communication, Sept. 1957.

[4] Russell, P. F.: The present status of malaria in the world, Am. J. Trop. Med. and Hyg. **1**: 111, 1952.

[5] Russell, P. F.: World-wide malaria distribution, prevalence and control, Am. J. Trop. Med. and Hyg. **5**: 937, 1956.

[6] Presidential Address to Congress on May 22, 1957, Mutual Security Act of 1957 (S. 2130) section 420 on malaria eradication.

[7] Boyd, M. F.: Malariology, 1949, W. B. Saunders Co., Philadelphia, p. 3.

[8] Boyd, M.: A symposium on human malaria, Pub. of the A.A.A.S. No. 15, 1951, Historical Introduction, Science Press, Lancaster, Pa., p. 1–7.

[9] Ackerknecht, E. H.: Malaria, Ciba Symposia **7**: 38–68, 1945.

[10] Warshaw, L. J.: Malaria, the biography of a killer, 1949, Rinehart & Co., Inc., N. Y.

[11] Covell, G., Coatney, G. R., Field, J. W., and Singh, Jaswant: Chemotherapy of malaria, World Health Organization: Monograph Series No. 27, 1955.

received, it was soon amply confirmed, and for this work he was later (1907) awarded a Nobel prize.[12, 13]

In 1895 Ronald Ross, a member of the British Medical Corps assigned to India, began his study of mosquitoes and malaria, doubtless stimulated by the suggestion of Sir Patrick Manson (1894) that mosquitoes could be the transmitting agent. In 1897 he finally demonstrated the parasites in the stomach wall of the Culex mosquitoes. As Manson remarked, "Ross has hammered out the key, others might take the trouble to open the door." [12, 14, 15] This, the actual experimental transmission of the disease to man by the Anopheles mosquito, was first accomplished in 1898 by Bignani, Bastianelli and Grassi.[7] Important contributions were made by numerous other observers before and after these crucial studies, including many in this country.[10, 16, 17, 18, 19, 20]

Historical evidence suggests that before the exploration and settling of North America, a state of anophelism without malaria existed in this country.[25] Malaria may have been introduced into the East Coast of North America by the early settlers from the low swampy land of certain counties in England. The disease was endemic there in the sixteenth and seventeenth centuries, and malaria was called the "Kentish disorder." [25] Early French and Spanish settlers along the Gulf Coast may have provided the source for the original infection in the deep south and in the lower Mississippi valley. When Negro slaves were imported from Africa into the American colonies for the cultivation of rice and sugar cane, the incidence of malaria increased. These slaves were probably heavily infected. The cultivation of rice and sugar cane also resulted in the stagnation of much water and thus increased

[12] Bloomfield, A. L.: A bibliography of internal medicine: Malaria, J. Chron. Dis. 1: 665, 1955.

[13] Laveran, A.: Note sur un noveau parasite trouvé dans le sange de plusieurs malades atteints de fièvre palustre, Bull. Acad. Med. 19: 1235, 1880.

[14] Ross, Ronald: On some peculiar pigmented cells found in two mosquitoes fed on malarial blood, Brit. M. J. 2: 1786, 1897.

[15] Manson, Patrick: Experimental proof of the mosquito-malaria theory, Brit. M. J. 2: 949, 1900.

[16] Councilman, W. T., and Abbot, A. C.: A contribution to the pathology of malarial fever, Am. J. M. Sc. 89: 416, 1885.

[17] Councilman, W. T., and Abbot, A. C.: Certain elements found in the blood in cases of malarial fever, Tr. A. Am. Phys. 1: 89, 1886.

[18] MacCallum, W. G.: On the flagellated form of the malaria parasite, Lancet 2: 1240, 1897.

[19] King, A. F. A.: Insects and disease, mosquitoes and malaria, Pop. Sc. Month. 33: 644, 1883.

[20] Thayer, W. S., and Hewetson, J.: The malarial fevers of Baltimore, Johns Hopkins Hosp. Rep. 5: 3, 1895.

[21] Welch, W. H.: Malaria: definition, synonyms, history, parasitology, Loomis-Thompson, System of the Practice of Med., 1: 17, 1897, Lea Bros. & Co., New York.

[22] Russell, P. F.: Malaria: basic principles, 1952, Blackwell Scientific Publications, Oxford.

[23] Faust, E. C.: Clinical and public health aspects of malaria in the United States from an historical perspective, Am. J. Trop. Med. 25: 185, 1945.

[24] Freebor, S. B.: Anophelines of the nearctic region, *in* Malariology, by Boyd, W. B. Saunders & Co., Vol. 1, 1949, p. 379.

[25] Duffy, John: Epidemics in colonial America, 1953, Louisiana State University Press, p. 204–214.

anophelism. There is evidence that in 1684 malaria was well entrenched in Northern Canada. The French may have carried malaria into the Mississippi valley in their travel southward from Illinois to the mouth of the Mississippi River. It was well established here in 1700. Malaria was prevalent in all the North American colonies during the latter part of the seventeenth century.

In New England malaria spontaneously began to subside early and had practically disappeared by 1775. It increased rapidly, however, in the middle and southern colonies, gradually receding from the most northern colonies. New York City was the northernmost boundary for malaria by the outbreak of the Revolutionary War, whereas it had become hyperendemic from Georgia to Pennsylvania.

The spread of human traffic and settlements into the frontier lands associated with the indiscriminate clearing of forests and the artificial impounding of water in the more arid areas of the midwest resulted in increased breeding of mosquitoes and a higher density of anophelism. The railroad builders dug and abandoned borrow-pits alongside the tracks which during the rainy season became residual waterholes and increased the breeding of mosquitoes. Only later, when total and suitable cultivation of the land was undertaken and when low, wet areas were drained into natural waterways did the mosquito population decrease.[25]

The same phenomenon was observed a hundred years later in 1942 and 1943 when the U. S. Armed Forces first occupied the malaria-infested South Pacific Islands. The crude road building, the jeep and heavy artillery tracks, and the bomb craters coupled with 140 inches of rainfall a year caused an enormous increase in anophelism, resulting in epidemics of malaria. Malaria control became effective only some months later after the causes of this man-made increase in malaria had been corrected.[26]

By 1855 malaria had reached a peak and was endemic throughout the United States, with hyperendemic areas in the southeastern states. Malaria spread to the valleys of the Ohio, Illinois and Mississippi rivers by the westward trek of pioneers searching for new lands. This disease was an important but not a compelling deterrent to the settling of the American midwest. Shattuck stated in his report of the Sanitary Commission of 1849 that the "most common disease of all was malaria." [27] The Civil War gave a great impetus to the incidence of malaria, particularly in the impoverished South, and this continued into the post-war recovery period. During the Civil War over 50% of the troops were attacked annually by the disease. With the return of Federal troops to their northern homes, malaria again increased in both the north and northeast.

By 1870 agricultural reclamation of land by drainage of swamps, marshes

[26] Harper, P. A., Lisansky, E. T., et al.: Malaria and other insect-borne diseases in the South Pacific Campaign, 1942–1945, Supplement Am. J. Trop. Med. 27: 1–127, 1947.

[27] Winslow, C. E., and Smillie, W. G.: The history of American epidemiology, 1952, C. V. Mosby Co., St. Louis, p. 59.

and low-lands resulted in a diminution of malarial fevers. This treatment of the land, however, was no deliberate effort to control malaria or mosquitoes. The temperate climate of the northern United States with shortness of the season suitable for transmission by the mosquito contributed to a spontaneous remission of malaria in that section.

This is important because the northern boundary of the malaria belt began to contract prior to the discovery of the malaria plasmodium (1880) and of the mosquito vector (1886). Social, economic and agricultural advances unwittingly began to work for malaria control. Thus the malaria recession began spontaneously independent of purposeful antimalarial efforts. It was possibly associated with improved socio-economic conditions, such as better housing, improved sanitation, bonification of urban lands and agricultural drainage. More cattle breeding deviated mosquito feeding from man to animals.[28] Only two species of mosquito are important vectors in the United States: *Anopheles quadrimaculatus* in the eastern and central regions and *A. freeborni* in the western states. The females of both species have shown a progressively higher proportion of pig, horse, and cattle blood than of human blood in their stomach contents when examined by the precipitin test.

This malarial recession was also noticeable in the South coincident with the economic and social resurgence of that region. During the same time a similar spontaneous regression of malaria occurred in England, France and Germany. At the present time, in Malaya, malaria has been receding for the past ten years independent of any efforts at malaria control.[35]

Mosquito nets and screens were used quite early in the United States and may have contributed to the recession to some slight extent, although employed primarily for relief from the nuisance of insect bites. Wire screening, although introduced in 1850, was not extensively used until 1880. Before 1900 there was no deliberate program for control of malaria except for the use of quinine, which reduced the severity of the illness but not the attack rate.

Similarly the great epidemics of yellow fever, cholera, smallpox and typhoid fever in the United States began to subside before the cause, methods of prevention or specific treatment of any of these diseases was known.[30]

[28] Ackerknecht, E. H.: Malaria in the upper Mississippi valley 1760–1900, Supplement No. 4 to the Bulletin of History of Medicine, 1945.

[29] Andrews, J. M.: What's happening to malaria in the U. S. A., Am. J. Public Health **38**: 931, 1948.

[30] Smillie, W. G.: The period of great epidemics in the United States (1800–1875), 1952, C. V. Mosby Co., St. Louis, Chapter on History of American Epidemiology, p. 56.

[31] Winslow, C. E. A.: The conquest of epidemic disease, 1943, Princeton University Press, p. 236.

[32] Simmons, J. S., Callender, G. R., et al.: Malaria in Panama, 1939, the Johns Hopkins Press, Baltimore.

[33] Darrow: Am. J. Hygiene **50**: 207, 1949.

[34] Pampana, E. J.: Changing strategy in malaria control, Bull. World Health Organization **11**: 513–520, 1954.

[35] MacDonald, G.: Theory of the eradication of malaria, Bull. World Health Organization **15**: 289–401, 1956.

This occurred because of an improvement in social conditions. It was known as the time of "The Great Sanitary Awakening," [31] and it began to gain momentum slowly in the early eighteen-hundreds. It was concerned with common-sense community housekeeping. The Bacteriological Era (1876–1920) with its definitive medical discoveries decisively continued the job of ending the period of great epidemics in the United States.

In 1900 the first demonstration on a large scale of controlling malaria by abatement of mosquitoes was accomplished by William G. Gorgas in Havana, Cuba.[32] Gorgas exploited the growing knowledge of the epidemiology of malaria and began the earliest planned application of drainage of Anopheles breeding places as a malaria control measure. This was done during the American occupation of Cuba subsequent to 1900 and served as a testing of the program which assured his future victory over yellow fever and malaria in the Panama Canal Zone in 1905. Gorgas' main effort against the Anopheles mosquito was directed to the drainage of swamps, thus destroying potential and actual breeding places. Over eight million feet of ditching was completed for the purpose of drainage of water. He used mixtures of crude oil and kerosene to cover bodies of water which could not be drained. This killed the mosquito larvae, whose air spiracles just penetrate the surface film of water and thus become clogged with oil which is toxic to the tracheal cells. He also used top feeding minnows (gambusia) which feed on mosquito larvae.

The Canal Zone Bureaucracy and the Washington Governmental Administration offered a great obstacle to Gorgas since they thought that his drainage program was an exorbitant waste of money, and they ridiculed his insistence on the importance of the mosquito as a factor in transmission of the disease. Similarly fifty years later on Guadalcanal, malariologists were to hear high ranking commanding officers of American troops say depreciatingly "We are out here to fight Japs and to hell with the mosquitoes." [26]

Gorgas, Darling and others directed attention to the study of the biology of both adult and larval forms, including such things as their breeding habits, biting habits and range of flight. They found that different species of Anopheles required different environments and that the control of any one species which was a potent malarial vector could be accomplished more simply if one knew the precise biological requirements of that particular species. Another species of mosquito might require an entirely different type of attack.

In 1901 Ross did much the same thing in Freetown on the West African coast. He conducted mosquito surveys and suggested drainage and oiling of breeding pools. He designated his work crews as "Culex gangs" and "Anopheles gangs," each of which, when armed with the knowledge of the different biological requirements of these two species, was able intelligently to employ appropriate anti-mosquito measures.

Sir Malcolm Watson in 1901 while serving in Malaya made extensive surveys and discovered that *Anopheles maculatus,* the most important vector in that area, preferred to breed in clear, sunlit, running streams. He found that the degree of salinity, alkalinity or acidity of the water made a great difference in the survival and development of the mosquito larvae. In the United States the most important single naturalistic control measure has been the management of the water level of the T. V. A. Larval and pupal stages of the mosquito are stranded and killed by a cyclical weekly fluctuation of the water level during the heavy mosquito breeding season of the late summer.[38]

The most striking example of the eradication of a species of mosquito from a limited area is the elimination of *Anopheles gambiae* from South America. This virulent androphilic vector was accidentally transported from Dakar, Africa, to Natal, Brazil, by a fast French destroyer in 1930. It found an environment suited to its needs and soon caused a paralyzing epidemic of malaria. The indigenous mosquito vector had been a much less efficient transmitting agent and was primarily zoophilic, preferring animal blood. *A. gambiae* spread northward at the rate of 300 miles a year and in 1933 caused another explosive epidemic with 100,000 cases and 20,000 deaths. A campaign was initiated by the Brazilian government in collaboration with the Rockefeller Foundation for the complete extermination of *A. gambiae* in the Western Hemisphere. This was the first effort to eradicate a single species of mosquito from a large part of the world. The attack consisted of the elimination of breeding places and the simultaneous use of larvicides and spray insecticides to kill the adults.

In this Brazilian campaign, Paris Green, a double salt of arsenite and acetate of copper, as first advocated by Barber in 1921, was used as the larvicide. Used either as a dust or an oil solution, small particles of the toxicant float on the water and thus poison the surface feeding larvae. Pyrethrum powder was the chief toxic agent used against the adult mosquitoes. This insecticide, which is derived from the flowers of a chrysanthemum plant, was introduced into Europe from Persia and first manufactured in 1928. It had become popular as a household spray by 1930. It is a contact poison to which the nervous system of the adult insect is very vulnerable. Although it has only a negligible residual effect, it kills adult mosquitoes effectively and cheaply. Such use of this material was perhaps even more important than the larvicidal measures because the infected *A. gambiae* were shown largely to be found indoors.

The alteration or elimination of breeding places by drainage and the larvicidal measures which have been reviewed are rather expensive methods, although still useful in certain areas of the world. Experience has shown that malaria control is more effective and more economical when appropriate measures are directed against the infected adult insects rather than the larvae. The value of space sprays, such as pyrethrum, has been noted. Russell

has stated that "No doubt the almost universal use of such sprays in the southern United States in the 1930's and 1940's helped materially to reduce the incidence of malaria to its present near vanishing point." [22] Forty million one pound aerosol pyrethrum bombs were supplied to the allied armed forces during World War II. Space spraying kills flying or resting mosquitoes by contact with the insecticide at the time of spraying.

The practice of residual spraying marked an important advance in malaria control measures.[22, 24] D.D.T., used as an adulticidal spray or paint, has been especially important since it maintains a prolonged lethal effect on the insects for from three to six months after a single application to a surface, depending upon the formula used. The D.D.T. particles cling to a surface such as a wall or ceiling, and the mosquitoes which later come to rest on the surface are poisoned by contact and die. Mosquitoes which rest on such a surface for 10 to 30 minutes will die in from two to 24 hours. Residual spraying is found to be most effective when the inside walls and ceilings of all rooms in the homes of the malarious community are so sprayed. If an adult mosquito rests but once on such a sprayed surface and takes up a lethal dose of D.D.T. at any time during the interval required for the development of sporozoites following an infecting blood meal (usually 10 to 20 days, depending upon the environmental temperature), transmission of malaria by that mosquito will be prevented. Most anopheline vectors of malaria enter houses to feed upon man, and after biting rest upon the wall or ceiling. Thus the insects, laden with immature noninfective parasites, will be destroyed before the plasmodia can mature into infective sporozoites. Contact with residual D.D.T. which is not quickly lethal will reduce the longevity of mosquitoes so that ovipositing will be interfered with. The biting rate is also markedly reduced. This interruption of the transmission of malaria parasites will occur regardless of the number of larval or adult Anopheles outside of the houses. The aim is not to destroy all Anopheles mosquitoes but only those which are inside homes and infected with parasites, and therefore are potential transmitters. Eradication of malaria, therefore, can be accomplished at a reasonable cost, even though extermination of the mosquito vector may be neither possible nor economically feasible.[2]

Other adulticides having residual action have been developed, such as benzine hexachloride, chlordane and dieldrin.

A new problem has arisen, however, with the development of resistance by the insects to these residual toxicants.[36] The present generations of some species of house flies, Culex and even Anopheles mosquitoes are not so readily killed by these insecticides as were earlier ones before exposure had occurred. Flies have become resistant to D.D.T. after one to three seasonal sprayings. Furthermore an acquired resistance in successive generations may extend from one to other chlorinated hydrocarbons, and the flies and mosquitoes may become tolerant to any of these toxicants.

[36] Busvine, J. R.: The significance of insecticide resistant strains, Bull. World Health Organization 15: 289–401, 1956.

Two types of resistance may occur, of which both have been described for mosquitoes. In one case, "physiological resistance" denotes the developed capacity in a given strain of mosquito to tolerate contact with a poison after previous generations have had contact with it. The use of "developed" in this sense indicates the appearance and progressive increase in tolerance or resistance to a poison in successive generations of a given strain or species of mosquito after previous generations had been extensively exposed to it and had suffered a selective mortality as a result. A more resistant race results from "the survival of the fittest."

In the second case, "behavioristic resistance" denotes the developed and transmitted tendency to avoid coming into contact with the poison after previous generations had been exposed to it.

Several recent articles deal with the problem of resistance and how it may be met.[36, 37] Some believe that the simultaneous use of a toxicant as a larvicide and an adulticide increases the probability of the development of resistance. It has been suggested that increasing the dose of the insecticide, changing from one insecticide to another, or using mixtures of insecticides may alter the development of resistance. Much more experimental work is needed. Reports are conflicting regarding the time required for the development of resistance,[37, 38, 39] but it appears likely that usually at least several years of exposure to an insecticide are required.

By efficient residual spraying over wide areas, interruption of the transmission of malaria could result in the elimination of malaria parasites from a region before resistance to the insecticide has been able to develop. The Bulletin of the World Health Organization of 1954 recommended the plan of discontinuing residual spraying after a few years, prior to the development of resistance in mosquito vectors.[34] This strategy offers a more realistic approach to the goal of "eradicating" rather than indefinitely "controlling" malaria and, it is hoped, may circumvent the development of resistant strains of Anopheles. The Eighth World Health Assembly has adopted this new anti-malaria policy. After the discontinuation of spraying, responsibility for the control of malaria would be assumed by a "System of Surveillance" of an area for any possible residual cases of primary indigenous malaria or any newly imported cases. The surveillance program would include the immediate investigation of the origin, the epidemiology and the possible vector of any suspected case of malaria.[40]

It has been suggested by Justin Andrews [8] that eradication of malaria involves reduction of cases to such a small number that the disease can not

[37] Garrett-Jones, C., and Gramiccia, G.: Development of resistance to D.D.T. by *Anopheles sacharove*, Bull. World Health Organization **11**: 185–883, 1954.

[38] Expert Committee on Malaria, Fifth Report, World Health Organization Technical Report Series No. 80, p. 5, 1954.

[39] Livadas, G. A., and Thymakis, K.: Susceptibility of malaria vectors to D.D.T. in Greece, Bull. World Health Organization **15**: 403–413, 1956.

[40] Andrews, J. M., Grant, J. S., and Fritz, R. F.: Effects of suspended residual spraying and of imported malaria on malaria control in the U. S. A. **11**: 839–848, 1954.

be maintained in a given area. This requires complete coverage of an adequately extended area by residual spraying for four years followed by a surveillance system for the next four years to find and eliminate any residual foci of malaria as well as possible newly imported cases. More expensive and laborious though time-honored methods of control could be avoided were this policy vigorously employed. The continued indiscriminate residual spraying of adulticides and larvicides should be avoided.

This goal of malaria "eradication" stands in sharp contrast to the previous policy of "control," which implies such a reduction in the number of cases of malaria in an area that it is no longer a serious health problem.[41] Malaria can not perpetuate itself in a given area when for three consecutive years there has been no transmission of parasites from person to person by mosquitoes. Contrary to popular belief, malaria infections of man do not last long, even if untreated. With few exceptions falciparum infections do not last longer than one year and vivax infections longer than two or three years. If no new primary indigenous cases of malaria occur in a community for three years, it may be considered free of malaria infection in both man and mosquito, despite the persistence of anophelism. Infection with *P. malariae* may last longer, but this species is rare, occurs in only small scattered areas over the world and practically is less important.[34]

The drugs commonly used—quinine, quinacrine (atabrine), chloroquine, camoquine—suppress the manifestations of malaria but do not cure vivax infections. Primaquine if administered under adequate supervision will eliminate both trophozoites and gametocytes of falciparum and vivax malaria. Drug prophylaxis as a major factor in malaria control, however, has serious biological, economic and administrative limitations and is justified only as an adjuvant and emergency method when malaria can not be immediately controlled by measures directed against the Anopheles mosquito.[1, 11]

Malaria has been eliminated entirely from large areas in the following countries or islands:[8] Corsica, Cyprus, Italy, Ceylon, Mauritius, Argentina, Chili, Venezuela, British Guiana, Panama Canal Zone, Puerto Rico, Barbados, Martinique.

This has been accomplished by a residual spraying in a nation-wide campaign vigorously employed for a definite period of time and then discontinued.

It is believed that eradication can be accomplished in a period of eight to ten years with no more than four to six years of spraying without danger of developing resistance. Certain requirements must be met, however, before residual insecticide spraying may be discontinued.[34] The parasite rate among the infant population should be determined as an index of the transmission of malaria. Blood smears from every case of questionable fever should be examined for a year before spraying is discontinued. The

[41] Andrews, J. M.: The eradication program in the U. S. A., J. Nat. Malaria Soc. **10**: 99–123, 1951.

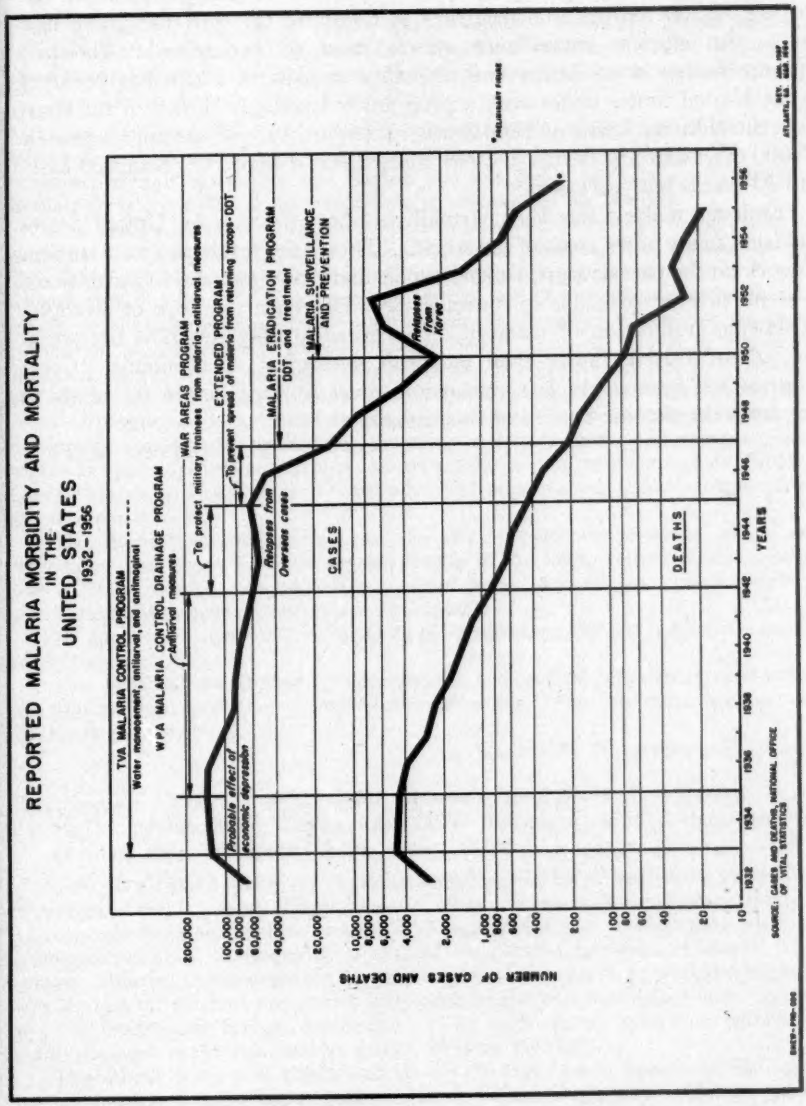
REPORTED MALARIA MORBIDITY AND MORTALITY
IN THE
UNITED STATES
1932-1956
TVA MALARIA CONTROL PROGRAM
Water management, antilarval, and antimalarial
WPA MALARIA CONTROL DRAINAGE PROGRAM
Antilarval measures
WAR AREAS PROGRAM
To protect military trainees from malaria - antilarval measures
EXTENDED PROGRAM
To prevent spread of malaria from returning troops - DDT
MALARIA ERADICATION PROGRAM
DDT and treatment
MALARIA SURVEILLANCE AND PREVENTION
Probable effect of economic depression
Relapses from Overseas cases
Relapses from Korea
CASES
DEATHS
NUMBER OF CASES AND DEATHS
YEARS
SOURCE: CASES AND DEATHS, NATIONAL OFFICE OF VITAL STATISTICS

FIG. 1.

control procedures should be conducted simultaneously over large areas, utilizing if possible natural geographic boundaries or contiguous areas employing similar antimalarial measures to minimize the introduction of new cases. An efficient surveillance system must be maintained. The precipitous decline in morbidity and mortality in malaria which has occurred in the United States under such a program is strikingly shown in the chart from the National Office of Vital Statistics (figure 1). From approximately 40,000 cases and 350 deaths in 1946, malaria has dropped to about 200 cases and 20 deaths ten years later.

Endemic malaria has been virtually eradicated from the United States and from many other areas of the world. This is the result of a vast amount of work on the part of a great many people and many national organizations. It seems not unreasonable to continue these efforts in the hope of attaining worldwide eradication of malaria. The principal obstacles now are social and administrative rather than technical, biological or economic. Great progress has been made, but much more must be done before the world is free from the chronic burden of this disease.[1, 3, 5]

E. Lisansky, M.D.

REVIEWS

Some Clinical Applications of Electroneurophysiology, Especially Electrodiagnosis and Electromyography. Volume I of Physical Medicine Library. Edited by SIDNEY LICHT, M.D. 272 pages; 15.5 × 23.5 cm. Elizabeth Licht, Publisher, New Haven, Conn. 1956. Price, $10.00.

This publication adequately describes two methods included in the battery of testing procedures used in the diagnosis of peripheral nerve pathology. A group composed of eight American, two English and two Swiss physicians well qualified in these areas contribute to the comprehensive coverage of the subjects.

The history of the application of electricity in neuromuscular investigation is presented as an inclusive discussion of neuromuscular physiology. A condensation of the theory and instrumentation employed in diagnosis by electrical currents is sufficiently informative. Routine electrical testing technics employing galvanic and faradic or alternating sinusoidal currents in order to determine whether or not there is reaction of degeneration are described in detail. A good resumé of Strength-Duration Curves which not only afford reaction of degeneration indices (rheobase and chronaxy) but also provide a more reliable assessment of regeneration and recovery progress of lower motor neuron lesions is given. The discussion of electromyography includes the method for detecting such neurogenic and myogenic disorders as: poliomyelitis, amyotrophic lateral sclerosis, progressive muscular atrophy, Guillain-Barre syndrome, nerve degeneration and regeneration, muscular dystrophies and myotonias.

The strength-duration curves and the electromyographic tracings which are reproduced from actual case records are helpful in the interpretation of test results. The charts of normal chronaxy values, motor points, dermatomes, cutaneous nerve distribution and segmental innervation are valuable.

An appendix includes a brief synopsis of encephalography and a brief discussion of electroretinography.

This book can be utilized by neurologists, orthopedists, physiatrists and other practitioners who encounter neuromuscular disorders. The references are for the most part quite adequate.

GLADYS E. WADSWORTH, Ph.D.

Cryptococcosis: Torulosis or European Blastomycosis. By M. L. LITTMAN, M.D., Ph.D., and LORENZ E. ZIMMERMAN, M.D. 205 pages; 26 × 18 cm. Grune & Stratton, Inc., New York. 1956. Price, $8.50.

There is no doubt that every physician now has need for an increasing knowledge of mycotic diseases. Also, intense research long overdue in this important facet of microbiology must be rapidly advanced if clinical medicine is to keep pace with the mycologic problems so frequently a part of complicated infectious diseases. This volume, dedicated to one organism, is an example of what might be produced through careful study of existing literature. This book might well stimulate similar studies of other troublesome biologic malefactors. The study covers only data pertaining to *Cryptococcus neoformans* and its disease in man, Torulosis.

The volume notes with clarity and brevity existing factual knowledge and summarizes important investigative aspects. Basic microbiologic and pathologic processes are well described, adequately illustrated and attractively presented. A very inclusive volume presenting just about everything of value known about Torulosis, it reflects careful and meticulous work. The central nervous system is particularly well illustrated and carefully studied. A section on cryptococcosis in animals is also

presented. Of particular interest is a chapter concerned with the biochemical features of torula. An appendix, including culture media and stains, is followed by an excellent and inclusive bibliography.

In an active scientific world where new facts accumulate so rapidly as often to engulf the unsolved problems, clear conceptual thinking is difficult to achieve. The scientific craftsmanship displayed by the authors in the building of such a valuable concept of the torula problem should not go without just praise.

The internist will find the volume a ready source for valuable clinical data. The investigator will find here much useful background information along with a provocative text. To the pathologist the book is a gem and a most valuable and useful addition to the monograph section of the working library.

J. A. W.

Clinical Use of Radioisotopes: A Manual of Technique. Edited by THEODORE FIELDS, M.S., F.A.C.R. (Assoc.), and LINDON SEED, M.D. 455 pages; 20 × 13.5 cm. The Year Book Publishers, Inc., Chicago. 1957. Price, $9.50.

This book is precisely that which its title indicates. It is a manual of practical technics in a relatively new specialty of clinical medicine. The authors did not attempt to compile all the known technics and their multitudinous variations. Only those procedures which are considered to be representative of the available clinical technics are critically reviewed. Individual sections are devoted to (1) clinical diagnostic procedures—their sources of error and their interpretation; (2) clinical therapeutic technics—their rationale, application, and limitations; (3) planning and operating the radioisotope laboratory—the problem of space, cost, and special instrumentation; and (4) radiation safety—the general and specific rules and recommendations aimed at the protection of laboratory personnel, hospital personnel, and patients.

It is a manual, well written, by contributors who are well qualified experts. With its comprehensive bibliography, excellent appendices, and adequate index this manual should prove to be a practical and valuable laboratory technic reference source for technician, trainee, and others engaged in clinical radioisotope laboratory activities.

R. E. BAUER, M.D.

Diagnosis and Treatment of Cardiovascular Disease. 5th Ed. Edited by WILLIAM D. STROUD, M.D., F.A.C.P., Professor of Cardiology, University of Pennsylvania Graduate School of Medicine, and MORRIS W. STROUD, III, M.D., Associate Professor of Medicine, Western Reserve University. Vol. I, 743 pages; Vol. II, 705 pages; 27 × 18.5 cm. (loose-leaf, leather bound). F. A. Davis Company, Philadelphia. 1957. Price, $35.00.

Fifty-nine outstanding authorities in cardiovascular disease in this country have contributed to this text, fifth edition of the *Diagnosis and Treatment of Cardiovascular Disease*. Looseleaf binding has been used with the plan continuously to revise the chapters in the light of newer concepts and advancements. The editors believe that the problem of cardiovascular disease has become so large and so complicated that it appears impossible for one man to write a completely satisfactory book on this subject.

Many of the chapters are noteworthy. The two chapters on cardiac surgery are particularly worthwhile, as written by Dr. Claude S. Beck and Dr. Robert P. Glover and Dr. Julio C. Davila. Among the other contributing authors are Drs. Edgar V. Allen, Rachel Ash, Nelson W. Barker, Samuel Bellet, William Dock, Franklin D. Johnston, Samuel A. Levine, Howard A. Rusk, Howard B. Sprague,

Paul D. White, Irving S. Wright, Charles C. Wolferth and many others. It is unfortunate that a few of the chapters have not been revised. Thus, some of the references are no more recent than 1940 in a field in which rapid advances have been made. A certain amount of overlap of material is to be expected and is of some value in a text such as this. In the discussion of "Arterial Hypertension," there are two chapters by different contributors, covering essentially the same material but with a difference of eight years in perspective. It is undoubtedly difficult in editing any text to allocate proportionate space to the many subjects which must be included. In this text of 1448 pages, the chapter of "Coronary Disease Including Angina Pectoris" comprises 22 pages. To electrocardiography are devoted almost 200 pages.

Many of the chapters in this text are outstanding. The selective reader will find much in these volumes of considerable value. The looseleaf form of binding should aid the editors in further additions and revisions as a practical means of keeping this text up to date.

L. S.

Epilepsy: Grand Mal, Petit Mal, Convulsions. By LETITIA FAIRFIELD, C.B.E., M.D., D.P.H. 159 pages; 19 × 12.5 cm. Philosophical Library, Inc., New York. 1957. Price, $4.75.

The author of this book has presented a short concise picture of epilepsy including a very short history, discussion of types of attacks, diagnostic procedures including use of electroencephalograms, causes, and prognosis. A short chapter is included on drug and diet treatment including the more recently used medicines. Then most of the book is concerned with the education and facilities available in England for the benefit of these individuals. One important point to note is the separation of individuals according to mental ability and removal of them from the mentally ill group into colonies for epileptics with a view toward readjustment back to society when seizures are controlled. There is a short chapter on laws as regards epilepsy in England. In the appendix is a group of the most common questions patients have asked with suggested answers which would be excellent for social workers to familiarize themselves with.

This book in general is a survey of English treatment of the epileptic. Due to the fact that so much of this book is devoted to colony and school treatment, it is not as helpful to the lay reader in this country as it would be to educators and social workers.

R. W. B.

Retrolental Fibroplasia Role of Oxygen: Report of the Sixteenth M & R Pediatric Research Conference. 62 pages; 15 × 23 cm. (paper-bound). Issued by M & R Laboratories, Columbus 16, Ohio. 1955. Available on request.

This illustrated symposium presents investigations of the toxicity of oxygen and the causes of retrolental fibroplasia. It seems certain that retrolental fibroplasia is produced in premature babies chiefly by administration of too much oxygen for too long. Other suspected contributing causes are discussed.

GRANGE S. COFFIN, M.D.

Clinical Electrocardiography: Interpretation on a Physiologic Basis. By MANUEL GARDBERG, M.D., with chapters by RICHARD ASHMAN, Ph.D., IRVING L. ROSEN, M.D., and LOUIS LEVY, II, M.D. 315 pages; 26 × 18 cm. Paul B. Hoeber, Inc., Medical Book Dept. of Harper & Brothers, New York. 1957. Price, $12.75.

There are now available numerous textbooks on electrocardiography each approaching the problems of electrocardiography in a somewhat different way. As

the author states in the preface of this text, "It is the ambitious purpose of this book to attempt to fill the need for a visual method that is based on a knowledge of physiologic principles. It is hoped that it will aid the medical student and practicing physician in interpretation of the electrocardiogram with greater accuracy and security." After introductory chapters on Electrical Phenomena of the Heart, Depolarization of the Ventricles, The Precordial Leads, T Wave, and Quantitative Analysis of QRS-T Relationships, other chapters are devoted to injury, ischemia, and specific electrocardiographic abnormalities. The contents are profusely illustrated with numerous excellent electrocardiographic reproductions. In many instances, serial tracings are available and one can follow the progression of changes over important periods of time. The author has employed numerous diagrams in an attempt by spatial representation to offer a physiologic basis for many of the electrocardiograms presented. These are at times extremely complex. Hypothetical spatial loops are employed as a means of elucidating various electrocardiographic abnormalities.

Although this book is ostensibly directed at the student and clinician, one wonders whether this aim is truly met. The general method of presentation appears too complex for both of these groups. Simplification of both the text and the diagrams would have materially increased the scope of applicability of this text.

L. S.

Tumors of the Female Sex Organs. Part I. Hydatidiform Mole and Choriocarcinoma (Atlas of Tumor Pathology, Section IX, Fascicle 33). By ARTHUR T. HERTIG, M.D., and HAZEL MANSELL, M.B., B.S. 63 pages; 26 × 20 cm. (paperbound). Published by the Armed Forces Institute of Pathology, under the auspices of the Subcommittee on Oncology of the Committee on Pathology of the National Research Council, Washington, D. C. Price, $1.00.

This represents one of a series of short atlases which are to be published by The Armed Forces Institute of Pathology, and this individual monograph may be obtained for $1.00. This seems the bargain of the year in view of the fact that the senior author is not only one of the eminent pathologists of this country, but has always been especially interested in these trophoblastic diseases. The junior author is acquiring increasing prominence by virtue of a number of important publications of her own, or in conjunction with Dr. Hertig.

This little treatise consists of 15 magnificent illustrations (some in color) preceded by a short (27 page) discussion of mole and choriocarcinoma. The pictures are reproduced beautifully, are of excellent choice and calibre, and are accompanied by legends which are brief but succinct. A preliminary chapter covers the most important problems of histogenesis, symptomatology, clinical behavior and prognosis in these bizarre diseases. The authors do not accept hydatidiform mole as a tumor, but as a degenerative form of missed abortion, and they present suggestive evidence. They rightfully emphasize the vagarious manner in which these lesions behave, but the reviewer cannot help but feel that they oversimplify the tremendous difficulties involved in the pathological diagnosis and clinical management of such cases. The late Dr. Emil Novak would approve of the authors' newer classification into apparently benign, potentially malignant, and apparently malignant patterns, for he was rather critical of a too rigid means of delineation in the older classifications.

To any one who has any pathological acumen this short treatise is a storehouse of material. How so much could be said and shown in so little space is amazing. It really ought to be required reading for every third or fourth year medical student, and there is no obstetrical or gynecological pathologist who will not profit from it. The authors deserve congratulations for one more excellent example of their always excellent work.

EDMUND R. NOVAK, M.D.

BOOKS RECENTLY RECEIVED

Books recently received are acknowledged in the following section. As far as practicable those of special interest will be selected for review later, but it is not possible to discuss all of them.

The Appraisal of Applicants to Medical Schools: Report of the Fourth Teaching Institute, Association of American Medical Colleges, Colorado Springs, Colorado, November 7–10, 1956. Edited by HELEN HOFER GEE and JOHN T. COWLES, with the assistance of the Planning Committee; editorial coordination by E. SHEPLEY NOURSE. 228 pages; 26 × 17 cm. 1957. Association of American Medical Colleges, Evanston, Illinois. Price, $3.00, cloth; $2.00, paper.

Biochemistry and Human Metabolism. 3d Ed. By BURNHAM S. WALKER, M.D., Ph.D., Associate Pathologist in Chemistry, Burbank Hospital, Fitchburg, Massachusetts, etc., WILLIAM C. BOYD, Ph.D., Professor of Immunochemistry, Boston University School of Medicine; and ISAAC ASIMOV, Ph.D., Associate Professor of Biochemistry, Boston University School of Medicine. 937 pages; 23.5 × 16 cm. 1957. The Williams & Wilkins Company, Baltimore. Price, $12.00.

Chronic Illness in a Large City: The Baltimore Study. Volume IV of *Chronic Illness in the United States.* Prepared by the COMMISSION ON CHRONIC ILLNESS. 620 pages; 24.5 × 16 cm. 1957. Published by the Harvard University Press, Cambridge, Massachusetts, for The Commonwealth Fund. Price, $8.00.

Handbook of Toxicology. WILLIAM S. SPECTOR, Editor. Volume II: *Antibiotics,* compiled from the literature by JOHN N. PORTER and GILBERT C. DE MELLO; prepared under the direction of the COMMITTEE ON THE HANDBOOK OF BIOLOGICAL DATA, Division of Biology and Agriculture, The National Academy of Sciences, The National Research Council, June, 1957, Aero Medical Laboratory Contract No. AF 33(616)–2873, Project No. 7159–71802, WADC Technical Report 55–16, Volume II, ASTIA Document No. AD 130959. 264 pages; 27.5 × 21 cm. (paper-bound). 1957. Published by Wright Air Development Center, Air Research and Development Command, United States Air Force, Wright-Patterson Air Force Base, Ohio. (May be purchased from W. B. Saunders Company, Philadelphia.)

Hormones in Blood. Volume II of *Ciba Foundation Colloquia on Endocrinology.* Editors for the Ciba Foundation: G. E. W. WOLSTENHOLME, O.B.E., M.A., M.B., B.Ch., and ELAINE C. P. MILLAR, A.H.–W.C., A.R.I.C. 416 pages; 21 × 14 cm. 1957. Little, Brown and Company, Boston. Price, $9.00.

Introduction to Protein Chemistry. By SIDNEY W. FOX, Professor in the Chemistry Department, Florida State University, etc.; and JOSEPH F. FOSTER, Professor of Chemistry, Purdue University. 459 pages; 23.5 × 15.5 cm. 1957. John Wiley & Sons, Inc., New York. Price, $9.00.

Manuale di Semeiotica Medica. Volume I. By F. LENZI and A. CANIGGIA. 593 pages; 26 × 18 cm. 1957. Edizioni Minerva Medica, Turin. Price, L. 7000.

Metabolic Aspects of Transport across Cell Membranes. Edited by Q. R. MURPHY. 379 pages; 24 × 16 cm. 1957. The University of Wisconsin Press, Madison. Price, $7.50.

The Physiologic Basis of Gastrointestinal Therapy. Selected Topics. By HEINRICH NECHELES, M.D., Ph.D., F.A.C.P., Director, Department of Gastro-Intestinal Research, Medical Research Institute of Michael Reese Hospital, etc.; and MARTIN M. KIRSHEN, M.D., F.A.C.P., Professor of Clinical Medicine, Chicago Medical School, etc. 330 pages; 22.5 × 14 cm. 1957. Grune & Stratton, New York. Price, $8.75.

The Physiology of Fishes. Volume II. *Behavior.* Edited by MARGARET E. BROWN, Department of Zoology, King's College, London. 526 pages; 23.5 × 16 cm. 1957. Academic Press, Inc., New York. Price, $14.00.

Practical Allergy. By M. COLEMAN HARRIS, M.D., F.A.C.P., Formerly Associate Clinical Professor of Internal Medicine (Allergy), College of Medical Evangelists, School of Medicine, Los Angeles, California, etc.; and NORMAN SHURE, M.D., M.S., F.A.C.P., Associate Clinical Professor of Internal Medicine (Allergy), College of Medical Evangelists, School of Medicine, etc. 471 pages; 24 × 16 cm. 1957. F. A. Davis Company, Philadelphia. Price, $7.50.

Psychological Implications of Current Pediatric Practice: Report of the Twenty-fourth Ross Pediatric Research Conference. 76 pages; 23 × 15 cm. (paper-bound). 1957. Ross Laboratories, Columbus, Ohio.

The Public Health Laboratory Service: First Report of the Expert Committee on Health Laboratory Methods. World Health Organization Technical Report Series No. 128. 49 pages; 24 × 16 cm. (paper-bound). 1957. World Health Organization, Geneva; available in U. S. A. from Columbia University Press, International Documents Service, New York. Price, 60¢.

A Textbook of Pharmacognosy. 7th Ed. By GEORGE EDWARD TREASE, B. Pharm., D. de l'U., F.P.S., F.R.I.C., F.L.S., Professor of Pharmacognosy, Director of Pharmaceutical Studies and Head of the Department of Pharmacy in the University of Nottingham. 808 pages; 22.5 × 14.5 cm. 1957. The Williams & Wilkins Company, Baltimore. Price, $8.50.

World Directory of Medical Schools. 2nd Ed. 314 pages; 24 × 16 cm. 1957. World Health Organization, Geneva; available in U. S. A. from Columbia University Press, International Documents Service, New York. Price, $5.00.